Acta Poloniae Pharmaceutica – Drug Research, Vol. 70 No.1 pp. 99–110, 2013 ISSN 0001-6837
Polish Pharmaceutical Society

DRUG SYNTHESIS

SYNTHESIS AND ANTIVIRAL EVALUTION OF SOME NOVEL PYRAZOLES AND PYRAZOLO[3,4-d]PYRIDAZINES BEARING 5,6,7,8-TETRAHYDRONAPHTHALENE

NEHAL A. HAMDY[1]* and WALED M. EL-SENOUSY[2]

[1] Applied Organic Chemistry Department, National Research Centre, Dokki 12622, Cairo, Egypt
[2] Enteric Viruses Laboratory, Center of Excellence for Advanced Sciences, National Research Centre, Dokki 12622, Cairo, Egypt

Abstract: The enaminone **2** was reacted with hydrazonyl halides **3a–d** to afford the corresponding pyrazole derivatives (**6a–d**) which reacted with hydrazine hydrate to afford the new pyrazolo[3,4-*d*]pyridazine derivatives **7a–d**, respectively. In addition, compound **2** was reacted with some primary aromatic amines to afford the corresponding secondary enaminones **10a–c** and reacted with sulfapyridine or sulfapyrimidine to afford the corresponding sulfonamide derivatives **12a** and **12b**. Evaluation of these new compounds against rotavirus Wa strain and adenovirus type 7 showed promising antiviral activity.

Keywords: enaminone, pyrazole, pyrazolo[3,4-d]pyridazine, sulfonamide, antiviral activity

Enaminone derivatives are highly reactive intermediates and are extensively used for the synthesis of a wide variety of biologically active heterocyclic systems (1–4). On the other hand, pyrazole derivatives are well established in the literatures as important biologically effective heterocyclic compounds. They act as anti-inflammatory (5), antipyretic (6), antimicrobial (7), antiviral (8–10), antitumor (11), anticonvulsant (12), antihistaminic (13), antidepressant (14), and potential agents against A549 lung cancer cells (15, 16).

Recently, some arylpyrazoles were reported to have non-nucleoside HIV-1 reverse transcriptase inhibitor activity (17). Moreover, some pyrazolopyridazines are good anti-inflammatory agents (18), potent inhibitors of glycogen synthase kinase-3 (GSK-3) (19) and selective cyclin dependent kinase (CDK4) inhibitors (20). Furthermore, sulfonamide derivatives were recently reported to be useful in targeting cancer chemotherapy (21, 22).

In addition, tetralins (tetrahydronaphthalene derivatives) are of increasing interest due to their vital role in the biological activities, as potent agonists for D_2-type receptors (23) Also, many tetralin analogues showed good efficiency in the treatment of Alzheimer's disease (24) cardiovascular diseases (25), anti-inflammatory diseases (26) and prevention of dopamine induced cell death (27).

Adenovirus type 7 (Ad 7) belongs to the *Adenoviridae* family. It contains linear, double stranded DNA ranged between 30000–42000 nucleotides long. It has icosahedral morphology and no envelope. Adenovirus (Ad) infections cause pneumonia and disseminated disease in both immunocompromised and nonimmunocompromised hosts. The human *Adenoviridae* contains 51 known serotypes defined by immunological methods and are categorized into six subgroups (A–F) based on common hemagglutination and DNA sequences. Human Ad7 belongs to subgroup B. In humans, subgroup B Ad, especially the species B 1 which contain Ad7, causes particularly severe lower respiratory tract infections. Ad infections are the most common cause of febrile respiratory tract infection and pneumonia in military recruits and have been responsible for 90% of recruit hospitalizations for pneumonia. In young children, mortality rates of Ad7 pneumonia from particularly virulent strains reach 23 to 29%. Hence, Ad7 is a significant human pathogen and is especially problematic

* Corresponding author: e-mail: drnehalhamdy63@hotmail.com; fax: +20 203370931

among children and adults in crowded living conditions (28).

Rotavirus is a genus within the family *Reoviridae*. *Rotaviruses* are icosahedral 65–70 nm particles, nonenveloped (resistant to lipid solvents), and the capsid contains all enzymes for mRNA production. The rotavirus genome contains 11 segments of dsRNA, which have a size range of 0.6 to 3.3 kilobase pairs. Rotaviruses are the single most important cause of severe diarrhea illness in infants and young children in both developed and developing countries worldwide. Although diarrheal diseases are one of the most common illnesses in this age group throughout the world, they assume a special significance in developing countries, where they constitute a major cause of mortality among the young children (29).

In recent year we developed new synthetic approaches for the construction of biologically active heterocyclic compounds (26, 30–32). Taking into consideration that there are no drugs for adenovirus type 7 and rotavirus Wa strain, the goal of the present work was directed to synthesize novel derivatives of tetralin attached to pyrazolo, pyrazolo[3,4-*d*]pyridazine, secondary enaminone and sulfonamide ring systems and to evaluate their antiviral activities.

EXPERIMENTAL

Chemistry

All melting points were measured using an Electro-thermal IA 9100 apparatus (Shimadzu, Japan). Microanalytical data were performed by Vario El-Mentar apparatus (Shimadzu, Japan), National Research Centre, Cairo, Egypt. IR spectra were recorded on a Biorad FTS 155 FT-IR spectrophotometer (ICB-IR Service Centre, Pozzuoli, Italy) or recorded as potassium bromide pellets on a Perkin-Elmer 1650 Spectrophotometer. ^{1}H-NMR experiments were conducted at ICB-NMR Service Centre (Pozzuoli, Naples, Italy), and were acquired in DMSO, (shifts are referenced to the solvent signal) on a Bruker Avance-400 apparatus operating at 400 MHz, and/or ^{1}H-NMR spectra were determined in DMSO-d_6 at 300 MHz (^{1}H-NMR) and at 75 MHz (^{13}C-NMR) on a Varian Mercury VX 300 NMR spectrometer using TMS as an internal standard (Faculty of Science, Cairo University, Cairo, Egypt). Mass spectra were carried out on an ion-trap MS instrument in EI mode at 70 eV (ICB-IR Service Centre, Pozzuoli, Naples, Italy), or determined on Shimadzu GCMS-QP-1000EX mass spectrometer at 70 eV (Cairo University, Cairo, Egypt).

Compounds **1** (33) and **3a–d** (34) were prepared as reported in the literature. Aromatic amines, sulfapyridine **12a** and sulfapyrimidine **12b** were used as commercially obtained.

E-3-(N,N-dimethylamino)-1-(5,6,7,8-tetrahydronaphthalen-2-yl)prop-2-en-1-one (2)

To a mixture of 2-acetyltetralin (**1**) (1.74 g, 10 mmol) in dry toluene (50 mL), dimethylformamide dimethylacetal (DMF-DMA) (1.34 g, 10 mmol) was added and the mixture was refluxed for 5 h. The solvent was evaporated and the residual reddish brown viscous liquid was taken in ether. The resulting yellow crystals were collected by filtration, washed thoroughly with ether, dried and finally recrystallized from EtOH to afford compound **2** as yellow crystals in 58% yield, m.p. 70–72^{o}C. IR (KBr, cm^{-1}): 1634 (C=O). ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.71 (m, 4H, alicyclic 2CH_2 of tetrahydronaphthalene), 2.72 (m, 4H, alicyclic 2CH_2 of tetrahydronaphthalene), 2.87 (s, 3H, CH_3), 3.10 (s, 3H, CH_3), 5.76 (d, 1H, J = 2.2 Hz, -CO-CH=), 7.05–7.58 (m, 3H Ar-H), 7.65 (d, 1H, J = 12.2 Hz, =CH-N-). ^{13}C-NMR (DMSO-d_6, δ, ppm): 20.12, 20.13 (2CH_3), 22.48, 22.597, 28.70, 28.75 (4CH_2), 90.93 (CO-CH=), 124.25, 127.67, 128.44, 136.17, 137.52, 139.62 (aromatic-C), 153.63 (=CH-N-), 185.70 (C=O); MS m/z (%): 229 (M^+, 92.4), 212 (99.0), 159 (43.5), 98 (100). Analysis: calcd. for $C_{15}H_{19}NO$ (229.32): C, 78.56; H, 8.35; N, 6.11%; found C, 78.24; H, 8.03; N, 6.28%.

General procedure for preparation of compounds (6a–d)

To a mixture of equimolar amounts of compound **2** (0.916 g, 4 mmol) and appropriate hydrazonyl chloride **3** (4 mmol) in dry toluene (25 mL), triethylamine (0.56 mL, 4 mmol) was added and the reaction mixture was refluxed for 4 h. The precipitated triethylamine hydrochloride was filtered off, and the filtrate was evaporated and the residue was triturated with ethanol. The solid products were collected by filtration and recrystallized from dioxane to afford the corresponding pyrazole derivatives **6a–d**.

1-[1-Phenyl-4-(5,6,7,8-tetrahydronaphthalene-2-carbonyl)-1H-pyrazol-3-yl]-ethanone (6a)

Yellow crystals, yield 79%, m.p. 146–148^{o}C; IR (KBr, cm^{-1}): 2931 (CH alicyclic), 1689 (C=O), 1642 (C=O), 1597 (C=N). ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.75 (m, 4H, alicyclic 2CH_2 of tetrahydronaphthalene), 2.57 (s, 3H, CH_3CO), 2.77 (m, 4H, alicyclic 2CH_2 of tetrahydronaphthalene), 7.18 (d, J = 7.8 Hz, 1H, Ar-H), 7.43–7.61 (m, 5H, Ar-H), 7.99 (d, J = 7.5 Hz, 2H, Ar-H), 8.95 (s, 1H, pyrazole-5-

CH). ^{13}C-NMR (DMSO-d_6, δ, ppm): 22.7, 29.5 ($4CH_2$), 27.5 (CH_3-CO), 107.5, 119.7, 125.5, 126.2, 126.8,128.8, 129.2, 129.3, 131.2, 132.4, 139.7, 140.5, 140.9, 148.7 (aromatic-C), 194.4, 196.5 (2CO). MS, m/z (%): 344 (M^+, 80), 213 (100), 159 (15). Analysis: calcd. for $C_{22}H_{20}N_2O_2$: C, 76.72; H, 5.85; N, 8.13%; found: C, 76.90; H, 5.81; N, 8.01%.

1-[4-(5,6,7,8-Tetrahydronaphthalene-2-carbonyl)-1-p-tolyl-1H-pyrazol-3-yl]-ethanone (6b)

Yellow crystals, yield 76%, m.p. 162–164°C; IR (KBr, cm^{-1}): 2931 (CH alicyclic), 1684 (C=O), 1650 (C=O), 1602 (C=N). ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.76 (m. 4H, alicyclic $2CH_2$ of tetrahydronaphthalene), 2.38 (s, 3H, CH_3), 2.56 (s, 3H, CH_3CO), 2.78 (m, 4H, alicyclic $2CH_2$ of tetrahydronaphthalene), 7.18 (d, *J* = 7.5 Hz, 1H, Ar-H), 7.38 (d, *J* = 8.7 Hz, 2H, Ar-H), 7.50 (d, *J* = 7.5 Hz, 1H, Ar-H), 7.86 (d, *J* = 8.4 Hz, 2H, Ar-H), 8.87 (s, 1H, pyrazole-5-CH). ^{13}C-NMR (DMSO-d_6, δ, ppm): 21.2 (CH_3), 22.7, 29.5 ($4CH_2$), 27.5 (CH_3-CO), 107.4, 119.2, 125.3, 126.5, 128.4, 129.4, 129.6, 132.1, 135.9, 136.5, 140.5, 140.6, 148.7 (aromatic-C), 194.4, 196.5 (2CO). MS, m/z (%): 358 (M^+, 53), 357 ($M^+ - 1$, 15), 227 (100), 159 (40), 131 (49), 130 (30). Analysis: calcd. for $C_{23}H_{22}N_2O_2$: C, 77.07; H, 6.19; N, 7.82%; found: C, 77.29; H, 6.10; N, 7.69%.

1-[1-(4-Chlorophenyl)-4-(5,6,7,8-tetrahydronaphthalene-2-carbonyl)-1H-pyrazol-3-yl]-ethanone (6c)

Yellow crystals, yield 73%, m.p. 180–182°C; IR (KBr, cm^{-1}): 2930 (CH alicyclic), 1687 (C=O), 1647 (C=O), 1602 (C=N). ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.75 (m. 4H, alicyclic $2CH_2$ of tetrahydronaphthalene), 2.56 (s, 3H, CH_3CO), 2.77 (m, 4H, alicyclic $2CH_2$ of tetrahydronaphthalene), 7.18 (d, *J* = 7.5 Hz, 2H, Ar-H), 7.51 (d, *J* = 7.5 Hz, 2H, Ar-H), 7.64–7.67 (m, 2H, Ar-H), 8.01–8.04 (m, 2H, Ar-H), 8.95 (s, 1H, pyrazole-5-CH). ^{13}C-NMR (DMSO-d_6, δ, ppm): 22.7, 29.5 ($4CH_2$), 27.6 (CH_3-CO), 108.4, 119.2, 125.3, 126.8, 128.4, 129.4, 129.9, 132.1, 135.9, 136.5, 140.5, 140.6, 148.7 (aromatic-C), 195.4, 196.5 (2CO). MS, m/z (%):380 ($M^+ + 2$, 27), 378 (M^+, 81), 249 (33), 247 (100), 159 (69), 131 (64), 129 (51), 128 (44). Analysis: calcd. for $C_{22}H_{19}ClN_2O_2$: C, 69.75; H, 5.25; N, 7.49%; found: C, 69.95; H, 5.20; N, 7.34%.

1-[1-(4-Methoxyphenyl)-4-(5,6,7,8-tetrahydronaphthalene-2-carbonyl)-1H-pyrazol-3-yl]-ethanone (6d)

Pale brown crystals, yield 67%, m.p. 140–142°C; IR (KBr, cm^{-1}): 2925 (CH alicyclic), 1681 (C=O), 1655 (C=O), 1604 (C=N). ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.76 (m. 4H, alicyclic $2CH_2$ of tetrahydronaphthalene), 2.55 (s, 3H, CH_3CO), 2.78 (m, 4H, alicyclic $2CH_2$ of tetrahydronaphthalene), 3.83 (s, 3H, OCH_3), 7.11–7.14 (m, 2H, Ar-H), 7.17 (d, *J* = 7.8 Hz, 1H, Ar-H), 7.48 (s, 1H, Ar-H), 7.50 (d, *J* = 7.8 Hz, 1H, Ar-H), 7.87–7.90 (m, 2H, Ar-H), 8.81 (s, 1H, pyrazole-5-CH). ^{13}C-NMR (DMSO-d_6, δ, ppm): 22.7, 29.5 ($4CH_2$), 27.5 (CH_3-CO), 55.5 (OCH_3), 107.4, 112.2, 125.3, 126.5, 128.4, 129.4, 129.6, 135.9, 136.5, 140.5, 140.6, 148.7, 158.1 (aromatic-C), 194.4, 196.6 (2CO). MS, m/z (%): 374 (M^+, 71), 242.8 (100), 229 (26), 159 (75), 158 (25), 131, (55), 130 (34). Analysis: calcd. for $C_{23}H_{22}N_2O_3$: C, 73.78; H, 5.92; N, 7.48%; found: C, 73.98; H, 5.84; N, 7.36%.

General procedure for preparation of compounds (7a–d)

A mixture of the appropriate pyrazole derivative **6a–d** (1 mmol) and hydrazine hydrate (80%, 0.2 mL) in absolute ethanol (20 mL) was refluxed for 1 h then allowed to cool. The precipitated product was collected by filtration, washed with ethanol and dried. Recrystallization from ethanol afforded the corresponding pyrazolo[3,4-*d*]pyridazine derivatives **7a–d**.

7-Methyl-2-phenyl-4-(5,6,7,8-tetrahydronaphthalen-2-yl)-2H-pyrazolo[3,4-d]pyridazine (7a)

White crystals, yield 92%, m.p. 180–182°C; IR (KBr, cm^{-1}): 2921 (CH alicyclic), 1591 (C=N). ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.80 (m. 4H, alicyclic $2CH_2$ of tetrahydronaphthalene), 2.82 (m, 4H, alicyclic $2CH_2$ of tetrahydronaphthalene), 2.87 (s, 3H, CH_3), 7.26 (d, *J* = 8.1 Hz, 1H, Ar-H), 7.54–7.68 (m, 3H, Ar-H), 7.87–7.91 (m, 2H, Ar-H), 8.19–8.23 (m, 2H, Ar-H), 9.56 (s, 1H, pyrazole-H). ^{13}C-NMR (DMSO-d_6, δ, ppm): 16.9 (CH_3), 22.7, 29.8 ($4CH_2$), 107.1, 119.9, 122.8, 126.2, 128.4, 129.3, 129.4, 130.2, 130.4, 136.0, 137.0, 140.5, 143.6, 153.5, 157.0 (aromatic-C). MS, m/z (%): 341 ($M^+ + 1$, 25), 340 (M^+, 81), 339 ($M^+ - 1$, 26), 158 (41), 142 (98), 128 (28), 142 (98), 77 (100). Analysis: calcd. for $C_{22}H_{20}N_4$: C, 77.62; H, 5.92; N, 16.46%; found: C, 77.87; H, 5.81; N, 16.32%.

7-Methyl-4-(5,6,7,8-tetrahydronaphthalen-2-yl)-2-p-tolyl-2*H*-pyrazolo[4,3-*d*]pyridazine (7b)

White crystals, yield 89%, m.p. 108–110°C; IR (KBr, cm^{-1}): 2925 (CH alicyclic), 1596 (C=N). ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.80 (m. 4H, alicyclic $2CH_2$ of tetrahydronaphthalene), 2.42 (s, 3H, CH_3), 2.82 (m, 4H, alicyclic $2CH_2$ of tetrahydro-

naphthalene), 2.89 (s, 3H, CH_3), 7.26 (d, J = 7.8 Hz, 1H, Ar-H), 7.43 (d, J = 8.4 Hz, 2H, Ar-H), 7.86–7.91 (m, 2H, Ar-H), 8.09 (d, J = 8.1 Hz, 2H, Ar-H), 9.49 (s, 1H, pyrazole-H). ^{13}C-NMR (DMSO-d_6, δ, ppm): 16.9, 21.3 ($2CH_3$), 22.7, 29.5 ($4CH_2$), 107.1, 119.9, 122.8, 125.2, 128.4, 129.6, 129.7, 131.2, 132.4, 136.0, 137.0, 140.5, 143.6, 153.8, 157.0 (aromatic-C). MS, m/z (%): 355 (M^+ + 1, 23), 354 (M^+, 97), 353 (M^+ – 1, 39), 156 (92), 128 (29), 91 (100). Analysis calcd. for $C_{23}H_{22}N_4$: C, 77.94; H, 6.26; N, 15.81%; found: C, 78.19; H, 6.15; N, 15.67%.

2-(4-Chlorophenyl)-7-methyl-4-(5,6,7,8-tetrahydronaphthalen-2-yl)-2H-pyrazolo[3,4-d]pyridazine (7c)

White crystals, yield 93%, m.p. 105–107°C; IR (KBr, cm^{-1}): 2925 (CH alicyclic), 1589 (C=N). ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.79 (m. 4H, alicyclic $2CH_2$ of tetrahydronaphthalene), 2.82 (m, 4H, alicyclic $2CH_2$ of tetrahydronaphthalene), 2.85 (s, 3H, CH_3), 7.24 (d, J = 7.8 Hz, 1H, Ar-H), 7.68–7.88 (m, 4H, Ar-H), 8.17–8.26 (m, 2H, Ar-H), 9.57 (s, 1H, pyrazole-H). ^{13}C-NMR (DMSO-d_6, δ, ppm): 17.0 (CH_3), 22.7, 29.5 ($4CH_2$), 109.1, 120.9, 122.8, 125.2, 129.4, 129.6, 129.7, 130.2, 132.4, 136.0, 137.3, 143.5, 145.6, 153.8, 157.0 (aromatic-C). MS, m/z (%): 376 (M^+ + 2, 31), 374 (M^+, 91), 176 (100) 159 (53). Analysis calcd. for $C_{22}H_{19}ClN_4$: C, 70.49; H, 5.11; N, 14.95%; found: C, 70.79; H, 5.01; N, 14.75%.

2-(4-Methoxyphenyl)-7-methyl-4-(5,6,7,8-tetrahydronaphthalen-2-yl)-2-p-tolyl-2H-pyrazolo[3,4-d]pyridazine (7d)

White crystals, yield 87%, m.p. 100–102°C; IR (KBr, cm^{-1}): 2927 (CH alicyclic), 1609 (C=N). ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.78 (m. 4H, alicyclic $2CH_2$ of tetrahydronaphthalene), 2.81 (m, 4H, alicyclic $2CH_2$ of tetrahydronaphthalene), 2.88 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 7.15–7.26 (m, 3H, Ar-H), 7.85–8.13 (m, 4H, Ar-H), 9.47 (s, 1H, pyrazole-H). ^{13}C-NMR (DMSO-d_6, δ, ppm): 16.6 (CH_3), 22.7, 29.6 ($4CH_2$), 55.6 (OCH_3), 107.1, 119.9, 122.8, 126.2, 128.4, 129.3, 129.4, 130.2, 136.0, 137.0, 140.5, 143.6, 153.5, 157.0, 158.2 (aromatic-C). MS, m/z (%): 371 (M^+ + 1, 27), 370 (M^+, 100). Analysis: calcd. for $C_{23}H_{22}N_4O$: C, 74.57; H, 5.99; N, 15.12%; found: C, 74.89; H, 5.84; N, 14.95%.

General procedure for preparation of compounds (10a–c)

To a mixture of enaminone **2** (1.15 g, 5 mmol) in acetic acid (20 mL), the appropriate primary aromatic amine namely (p-fluoroaniline, p-bromoaniline and 2,4-dimethoxyaniline) (5 mmol) was added and the reaction mixture was stirred for 3 h. The precipitated product was collected by filtration, washed with ethanol and recrystallized from acetic acid to afford the corresponding derivatives **10a–c**, respectively.

3-[4-Fluoro-phenylamino-1-(5,6,7,8-tetrahydronaphthalen-2-yl)]-propenone (10a)

Canary yellow crystals, yield 84%, m.p. 138–140°C, the ratio of *Z*/*E* conformers: 65/35; IR (KBr, cm^{-1}): 3222 (NH), 2931 (CH alicyclic), 1635 (C=O). ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.73 (m. 4H, alicyclic $2CH_2$ of tetrahydronaphthalene), 2.75 (m, 4H, alicyclic $2CH_2$ of tetrahydronaphthalene), 6.06 and 6.40 (d, J = 8.0 and 12.4 Hz, 1H, -COCH=, *Z* and *E* conformers), 7.13–8.05 (m, 8H, Ar-H + =CH-N-, *Z* and *E* conformers), 9.99 and 11.98 (d, J = 12.4 Hz, 1H, NH, D_2O exchangeable, Z and *E* conformers). ^{13}C-NMR (DMSO-d_6, δ, ppm): 22.42, 28.75, ($4CH_2$), 96.38 and 101.70 (-COCH=, *Z* and *E* conformers), 124.50, 128.09, 129.07, 135.48, 140.84, 141.35, 141.62, 141.70, 141.80, 162.25 (aromatic-C), 96.18, 196.18, 152.24, 97.20, 153.31 (-C=CH *Z* and *E* conformers), 189.50, 192.32 (C=O, *Z* and *E* conformers). MS, m/z (%): 295 (M^+, 30), 247 (21), 225 (100) 171 (10), 141 (8), 77 (6). Analysis: calcd. for $C_{19}H_{18}FNO$: C, 77.27; H, 6.14; N, 4.74%; found: C, 77.49; H, 6.04; N, 4.12%.

3-[4-Bromophenylamino-1-(5,6,7,8-tetrahydronaphthalen-2-yl)]-propenone (10b)

Canary yellow crystals, yield 86%, m.p. 204–206°C, the ratio of *Z*/*E* conformers: 56/44; IR (KBr, cm^{-1}): 3200 (NH), 2923 (CH alicyclic), 1635 (C=O). ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.73 (m. 4H, alicyclic $2CH_2$ of tetrahydronaphthalene), 2.75 (m, 4H, alicyclic $2CH_2$ of tetrahydronaphthalene), 6.10 and 6.43 (d, J = 8.0 and 12.4 Hz, 1H, -COCH=, *Z* and *E* conformers), 7.08–8.07 (m, 8H, Ar-H + =CH-N-, *Z* and *E* conformers), 10.19 and 11.96 (d, J = 12.4 Hz, 1H, NH, D_2O exchangeable, *Z* and *E* conformers). ^{13}C-NMR (DMSO-d_6, δ, ppm): 22.42, 28.75, ($4CH_2$), 96.38 and 101.70 (-COCH=, *Z* and *E* conformers), 97.20, 125.50, 128.59, 129.07, 135.48, 140.53, 141.35, 141.62, 141.70, 141.80, 152.25 (aromatic-C), 96.18, 152.24, 153.31 (-C=CH *Z* and *E* conformers), 189.50, 192,32 (C=O, *Z* and *E* conformers); MS, m/z (%): 358 (M^+ + 2, 80), 356 (M^+, 90), 225 (73) 183 (100). Analysis: calcd. for $C_{19}H_{18}BrNO$: C, 64.06; H, 5.09; N, 3.93%; found: C, 64.26; H, 5.01; N, 3.81%.

Z-3-[2,4-Dimethoxyphenylamino-1-(5,6,7,8-tetrahydronaphthalen-2-yl)]-propenone (10c)

Brown crystals, yield 78%, m.p. 106–108°C; IR (KBr, cm^{-1}): 3198 (NH), 2938 (CH alicyclic), 1625 (C=O). ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.74 (m. 4H, alicyclic $2CH_2$ of tetrahydronaphthalene), 2.76 (m, 4H, alicyclic $2CH_2$ of tetrahydronaphthalene), 3.75 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 6.03 (d, *J* = 7.8 Hz, 1H, -COCH=, *Z* conformer), 6.53–6.70 (m, 2H, Ar-H), 7.11–7.64 (m, 4H, Ar-H), 7.81 (dd, *J* = 7.8 Hz, 1H, =CH-N-, *Z* conformer), 12.18 (d, *J* = 12.6 Hz, 1H, NH, D_2O exchangeable). ^{13}C-NMR (DMSO-d_6, δ, ppm): 16.6 (CH_3), 22.7, 29.6 ($4CH_2$), 56.1 ($2OCH_3$), 100.4, 100.9, 109.4, 112.5, 126.1, 126.7, 129.0, 130.3, 136.4, 139.4, 140.3, 142.3, 146.7, 146.8, 150.6 (aromatic-C). MS, m/z (%) 338 (M^+ + 1, 24), 337 (M^+, 100). Analysis: calcd. for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 14.15%; found: C, 74.98; H, 6.77; N, 14.02%.

General procedure for preparation of compounds (12a, b)

A mixture of compound **2** (5 mmol) and 4-amino-*N*-pyridin-2-yl-benzenesulfonamide (**11a**), or 4-amino-*N*-pyrimidin-2-yl-benzenesulfonamide (**11b**) (5 mmol) in acetic acid (20 mL) was refluxed for 2 h, and then allowed to cool. The precipitated product was collected by filtration, washed with ethanol and recrystallized from acetic acid to afford sulfonamide derivatives **12a** and **12b**, respectively.

4-[3-Oxo-3-(5,6,7,8-tetrahydronaphthalen-2-yl)-propenylamino]-N-pyridin-2-yl-benzenesulfonamide (12a)

Yellow crystals, yield 76%, m.p. 240–242°C, the ratio of Z/*E* conformers: 46/54; IR (KBr, cm^{-1}): 3256, 3134 (2NH), 2930 (CH alicyclic), 1633 (C=O), 1588 (C=N). ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.73 (m. 4H, alicyclic $2CH_2$ of tetrahydronaphthalene), 2.75 (m, 4H, alicyclic $2CH_2$ of tetrahydronaphthalene), 6.17 and 6.50 (d, *J* = 8.4 and 12.8 Hz, 1H, -COCH=, *Z* and *E* conformers), 6.85–8.08 (m, 12H, Ar-H + =CH-N-, *Z* and *E* conformers), 10.30 and 11.96 (d, *J* = 12.4 Hz, 1H, NH, D_2O exchangeable, Z and *E* conformers), 11.56 (s, 1H, NH, D_2O exchangeable). ^{13}C-NMR (DMSO-d_6, δ, ppm): 22.45, 28.88 ($4CH_2$), 95.05 and 99.96 (-COCH=, *Z* and *E* conformers), 114.82, 115.78, 124.40, 127.92, 128.04, 128.71, 129.07, 129.17, 129.55, 135.33, 135.73, 136.78, 139.84, 140.05, 141.14, 143.41, 144.07, 152.85 (aromatic-C + =CH-N- *Z* and *E* conformers), 187.47, 190.09 (C=O, *Z* and *E* conformers). MS, m/z (%): 433 (M^+, 24), 369 (100). Analysis: calcd. for $C_{24}H_{23}N_3O_3S$: C, 66.49; H, 5.35; N, 9.69, S, 7.39%; found: C, 66.79; H, 5.27; N, 9.57, S, 7.29%.

4-[3-Oxo-3-(5,6,7,8-tetrahydronaphthalen-2-yl)-propenylamino]-N-pyrimidin-2-yl-benzenesulfonamide (12b)

Yellow crystals, yield 78%, m.p. 274–276°C, the ratio of *Z*/*E* conformers: 46/54; IR (KBr, cm^{-1}): 3286, 3109 (2NH), 2934 (CH alicyclic), 1637 (C=O), 1589 (C=N); ^{1}H-NMR (DMSO-d_6, δ, ppm): 1.73 (m. 4H, alicyclic $2CH_2$ of tetrahydronaphthalene), 2.75 (m, 4H, alicyclic $2CH_2$ of tetrahydronaphthalene), 6.19 and 6.52 (d, *J* = 8.4 and 12.8 Hz, 1H, -COCH=, *Z* and *E* conformers), 6.99–8.79 (m, 11H, Ar-H + =CH-N-, *Z* and *E* conformers), 10.42 (s, 1H, NH, D_2O exchangeable), 10.33 and 11.99 (d, *J* = 12.4 Hz, 1H, NH D_2O exchangeable, Z and *E* conformers). ^{13}C-NMR (DMSO-d_6, δ, ppm): 22.65, 28.80 ($4CH_2$), 94.85 and 98.96 (-C0CH=, *Z* and *E* conformers), 114.82, 115.78, 124.40, 128.04, 129.07, 129.55, 135.33, 136.78, 139.84, 140.05, 141.14, 143.41, 157.46, 169.45 (aromatic-C + =CH-N- *Z* and *E* conformers), 189.57, 192.00 (C=O, *Z* and *E* conformers). MS, m/z (%): 434 (M^+, 23), 433 (M^+ – 1, 10), 370 (100), 369 (97). Analysis: calcd. for $C_{23}H_{22}N_4O_3S$: C, 63.58; H, 5.10; N, 12.89; S, 7.38%; found: C, 63.89; H, 5.01; N, 12.78; S, 7.27%.

Antiviral activity

Cytotoxicity assay

All samples (100 mg) were dissolved in 500 µL of ethanol or acetic acid. Cell monolayers Hep2 and MA104 (obtained from The Holding Company for Biological Products & Vaccines VACSERA, Egypt) were trypsinized, washed with culture medium and plated in a 96-well flat bottomed plate with 5×10^3 cells per well for both cell lines. After 24 h incubation, each diluted (Greiner-Bio-One, Germany) tested material (10 fold dilutions of decontaminated samples which 12 µL of 100x of antibiotic, antimycotic mixture was added to 500 µL of each sample) was added to the appropriate wells and the plates were incubated for further 48 h at 37°C in a humidified incubator with 5% CO_2. The supernatants were removed from the wells and cell viability was evaluated using microscopical examination, trypan blue and the MTT technique (35–37). The results are obtained from triplicate assays with at least 5 extract concentrations. The percentage of cytotoxicity is calculated as [(A–B)/A] × 100, where A and B are the OD492 of untreated and of treated cells, respectively.

Antiviral test

The *in vitro* antiviral screening method was used to estimate the inhibition of the cytopathic effect (CPE) of the pure compound on MA104 and HEP-2 cell monolayers infected with rotavirus Wa strain with initial titre 1×10^6 PFU/mL (ATCC VR-2018, obtained by Prof. Dr. Albert Bosch, University of Barcelona, Spain) and adenovirus type 7 with initial titre 1×10^7 PFU/mL (obtained by Dr. Ali Fahmy, VACSERA, EGYPT) using the end-point titration technique (EPTT) (38). Confluent monolayers of MA104 and HEP-2 cells were grown in 96-well microtiter plates, which were infected with serial tenfold dilutions of rotavirus Wa strain and adenovirus type 7 suspensions, respectively. The viruses were allowed to adsorb for 60 min at 37°C. Then, serial twofold dilutions of the test compounds in maintenance medium, supplemented with 2% serum and antibiotic, were added. The plates were incubated at 37°C, and the viral cytopathic effect was recorded by light microscopy after 2 to 8 days. Virus suspensions are characterized by their virus titres, which are expressed as the smallest amount of virus capable of producing a reaction in the host cells. The antiviral activity is expressed as a reduction factor (RF), being the ratio of the viral titres in the virus control and in the presence of the maximal non-toxic dose of test substance.

MTT assay (antiviral colorimetric assay)

Both MA104 and Hep2 cell monolayers were grown in 96-well microtiter plates. Dilutions of the extracts, prepared as described above for the EPTT assay, were added 1 h before viral infection. Ten infectious doses of virus were added to each well and incubated at 37°C in humidified 5% CO_2 atmosphere for 48 h. Controls consisted of untreated infected, treated uninfected and untreated uninfected cells. Cell viability was evaluated by the MTT colorimetric technique (37). Briefly, the supernatants were removed from the wells and 28 µL of an MTT (Sigma) solution (2 mg/mL in PBS) was added to each well. The plates were incubated for 1.5 h at 37°C, and 130 µL of DMSO was added to the wells to dissolve the MTT crystals. The plates were placed on a shaker for 15 min and the optical density was determined at 492 nm (OD492) on a multiwell spectrophotometer. The 50% cytotoxic concentration (CC_{50}) of the test extract is defined as the concentration that reduces the OD492 of treated uninfected cells to 50% of that of untreated uninfected cells. The 50% antiviral effective concentration, i.e., 50% inhibitory concentration of the viral effect (IC_{50}) is expressed as the concentration that reduces the absorbance of infected cells to 50% when compared to infected cells and control cells. The percent protection is calculated as $[(A–B)/C–B)] \times 100$, where A, B and C are the OD492 of treated infected, untreated infected, and untreated uninfected cells, respectively.

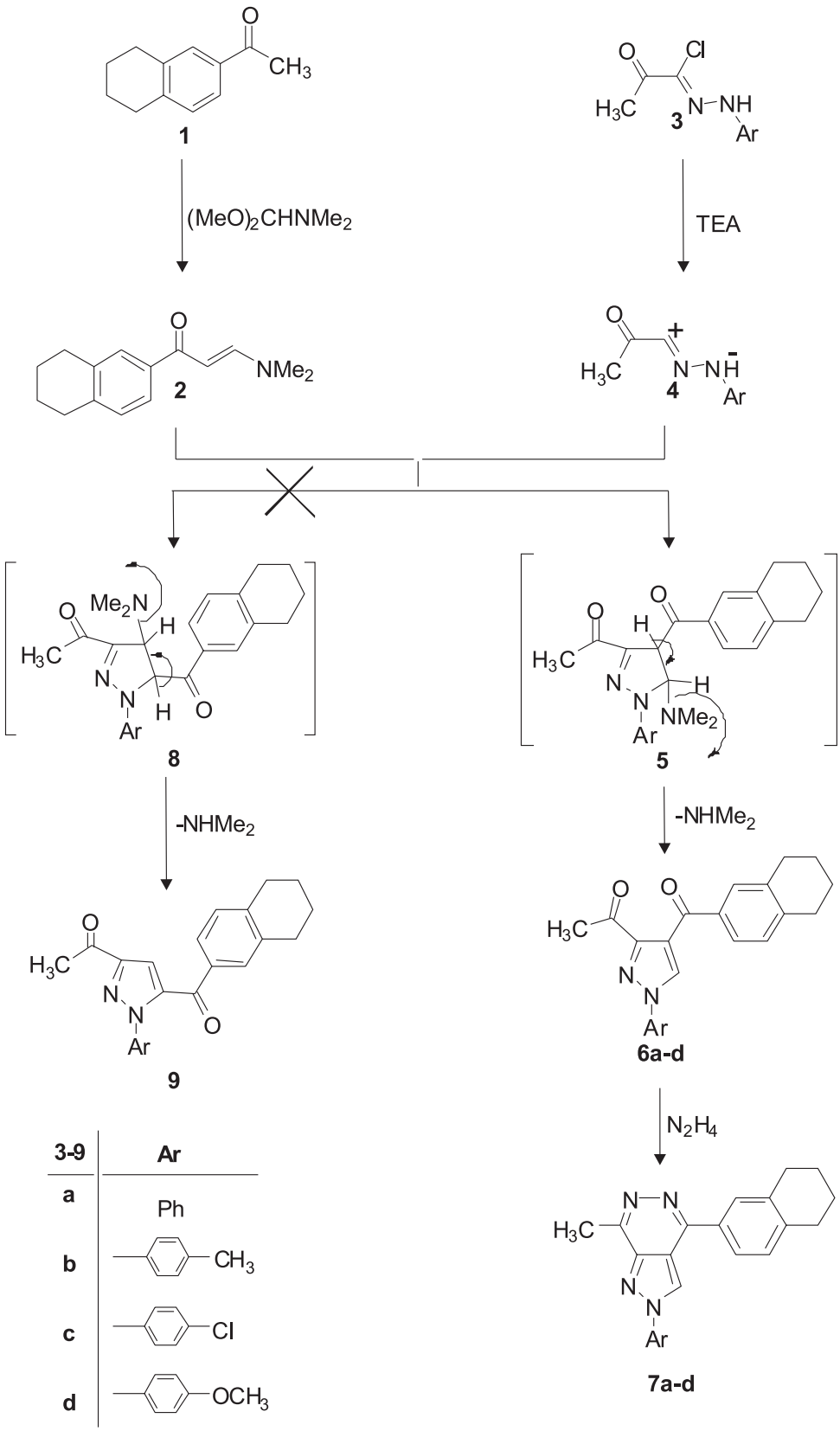
Data analysis

CC_{50} and IC_{50} for each compound were obtained from dose-effect-curves. The CC_{50} and IC_{50} are the average of four assays with 5 concentrations within the inhibitory range of the compound. The therapeutic index (i.e., selective index) is defined as CC_{50}/IC_{50}.

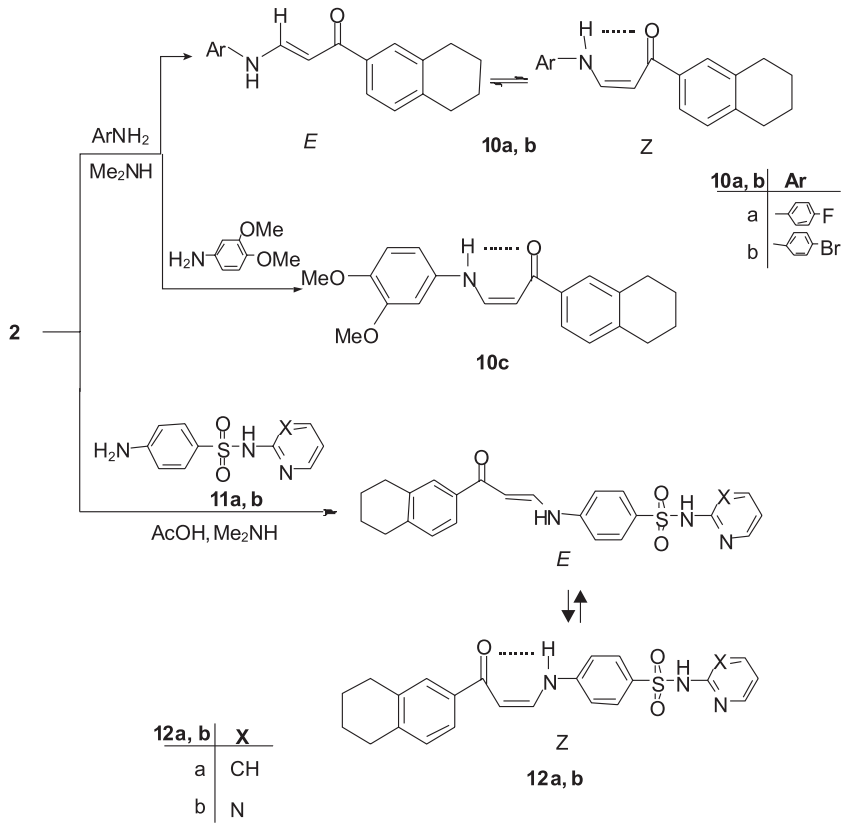
RESULTS AND DISCUSSION

Chemistry

Treatment of 2-acetyltetralin **1** (33) with dimethylformamide dimethylacetal (DMF-DMA) in refluxing dry toluene, afforded a yellow crystalline product that was identified as *E*-3-(*N*,*N*-dimethylamino)-1-(5,6,7,8-tetrahydronaphthalen-3-yl)prop-2-en-1-one (**2**) (Scheme 1). The structure of the isolated product was confirmed by elemental analyses and spectral data. ^{1}H-NMR spectrum displayed two singlets at δ 2.87, 3.10 ppm due to *N*,*N*-dimethyl protons and two doublets at δ 5.76 and 7.65 ppm (J = 12.2 Hz) due to the ethylenic protons, in addition to a multiplet at the region δ 7.05–7.58 ppm (3H, aromatics) and a multiplet at the region δ 1.71, 2.72 ppm for $4CH_2$ tetrahydronaphthalene protons. The value of the coupling constant (J = 12.2 Hz) for the ethylenic protons indicates that the enaminones **2** exists in the *E*-configuration, which was in complete agreement with results recently reported. (39, 40). 1,3-Dipolar cycloaddition of nitrilimines and nitrile oxides with alkenes is well documented (41, 42). Therefore, we studied now the regioselectivity in 1,3-dipolar cycloaddition of some nitrilimines **4a–d** with the enaminone **2**. Thus, the reaction of enaminone **2** with the nitrilimine **4a** (generated *in situ* by the action of triethylamine on the hydrazonyl chloride **3a**) in refluxing toluene afforded a single product (as examined by TLC and ^{1}H-NMR spectroscopy), for which the two regioisomeric cycloadducts **6a** and **9a** seemed possible. However, the regioisomer **6a** was assigned for the reaction product on the basis of its ^{1}H-NMR spectrum and its chemical *trans* formation outlined in Scheme 1. ^{1}H-NMR spectrum of the isolated product revealed two singlets at δ 2.57 and 8.95 ppm due to acetyl-CH_3 and pyrazole-5-CH protons, respectively, in addition to aromatic protons (m, 8H) in the region δ



Scheme 1. Synthesis of the intermediate **2** and target compounds **6a–d** and **7a–d**



Scheme 2. Synthesis of compounds **10a–c** and **12a, b**

7.18–7.99 ppm. The structure of compound **6a** was further confirmed by its reaction with hydrazine hydrate to afford a high yield of a white crystalline product, which was identified as 7-methyl-2-phenyl-4-(5,6,7,8-tetrahydronaphthalen-2-yl)-2*H*-pyrazolo[3,4-*d*]pyridazine (**7a**) (Scheme 1). The formation of the 5-unsubstituted pyrazole **6a** is assumed to take place *via* a regioselective 1,3-cycloaddition of the nitrilimine intermediate **4a** to the enaminone **2** to form the nonisolable intermediate **5a**, which suffers elimination of dimethylamine under the reaction conditions yielding the pyrazole derivative **6a**. The other possible regioisomer **9a** is not observed throughout the reaction and was excluded on the basis of the spectral data of the isolated product. In the pyrazole ring system, C-4 is the most electron-rich carbon; thus, H-4 is expected to appear at a higher field, about δ 6.35 ppm. On the other hand, H-5 is linked to a carbon attached to a nitrogen atom and therefore, it is deshielded and appeared typically in the region δ 7.60–8.95 ppm. The ^{1}H-NMR spectrum of the isolated reaction product revealed a singlet signal at δ 8.95 ppm, which indicates the presence of the pyrazole H-5 rather than H-4 in the structure of the isolated product. This observation is also in accordance with that reported (39). Also IR spectrum of compound **6a** showed two carbonyl absorption bands at 1689 and 1642 cm^{-1}, which disappeared in IR spectrum of the product **7a** and ^{13}C-NMR spectrum of compound **7a**, is in agreement with its chemical structure.

Prompted by these results and in order to generalize this reaction, the enaminome **2** was allowed to react with nitrilimines **4b–d** under the same experimental conditions to afford the same corresponding pyrazole derivatives **6b–d**. The latter products underwent cyclocondensation upon treatment with hydrazine hydrate in refluxing ethanol to give the pyrazolo[3,4-*d*]pyridazine derivatives **7b–d** (Scheme 1). Structures of the products **6b–d** and **7b–d** were established on the basis of their elemental analyses and spectral data. The enaminone **2** reacted with primary aromatic amines, namely 4-fluoroaniline, 4-bromoaniline and 2,4-dimethoxyaniline, to yield condensation products with the elimination of dimethylamine as a single product in

each case as examined by TLC. The stereochemistry of the formed substituted secondary enaminone derivatives was assigned, in each case, based on the ^{1}H-NMR spectroscopy in dimethyl-d_6 sulfoxide solution. They exist in the *E*/*Z* geometric conjugation forms in **10a, b**, however, **10c** exist in the *Z*-isomer (Scheme 2). ^{1}H-NMR revealed two sets of doublet each belonging to the NH group of the *Z* and *E* conformers at δ 9.99, 10.19 ppm and at δ 11.98, 11.96 ppm, respectively, for a total of one proton indicating the presence of a mixture of *Z* and *E* forms of compounds **10a**, **b.** The upfield lines of –NH protons were assigned to *Z* conformer structure and downfield lines protons of the same group to *E* conformer of compounds **10a, b** (43). Moreover, the ^{1}H-NMR spectra of compounds **10a, b** showed additional two doublets derived from –COCH= group at δ 6.06, 6.10 ppm (*J* = 8.0 Hz) and at δ 6.40, 6.43 (*J* = 12.4Hz) ppm, respectively, each representing *Z* and *E* conformers for a total of one proton. The ratios of *Z* and *E* in each case were calculated by using ^{1}H-NMR data. This observation is also in accordance with the results in the literature (43, 44).

The downfield peak of the amino protons (δ 10.19–12.18 ppm) in compounds **10a–c** suggests the existence of an intramolecular hydrogen bond and therefore, a *cis* relationship between the NH and C=O group, and *Z*-configuration was deduced. The formation of the *Z*-isomer only in compound **10c** was proven by the coupling constants of the hydrogen atom attached on the double bond at δ 6.03 ppm (*J* = 7.8 Hz), 7.81 ppm (*J* = 7.8 Hz) and also by a distinct splitting of the H-atom on the amino group NH (*J* = 12.6 Hz) fixed *via* an intramolecular hydrogen bond (45).

Moreover, treatment of enaminone **2** with sulfapyridine **11a** or sulfapyrimidine **11b**, in refluxing acetic acid afforded the corresponding sulfonamide derivatives **12a** and **12b** (Scheme 2). IR spectra of the reaction products showed two absorption bands due to 2 NH groups in the region 3286–3104 cm^{-1} in addition to an absorption band of C=O group in the region 1633–1637 cm^{-1}. Their mass spectra showed a signal corresponding to the molecular ion peak. ^{1}H-NMR spectra revealed singlet signals at δ 11.56 and 10.42 ppm, respectively, for **12a** and **12b** assigned to SO_2-NH (D_2O exchangeable). The ratios of *Z*/*E* (46:54) in each case were calculated by using ^{1}H-NMR data. ^{13}C-NMR spectrum of compounds **12a, b** is in agreement with their chemical structures.

Antiviral screening

It is observed that some tested using EPTT technique compounds have high antiviral activity. The 1 $\log_{10}$ reduction (90%) in the initial viral titre

Table 1. Minimal non-toxic dose and anti-rotavirus Wa strain activity of tested compounds on MA104 cells determined by the end-point titration technique.

Tested compounds*	Viral reduction factor
6a	1
6b	1
6c	10
6d	10
7a	1
7b	1
7c	10
7d	10
10a	1
10b	10
10c	10
12a	10
12b	10

*Maximum non toxic dose for all the tested compounds = 0.1 mg/mL.

Table 2. Minimal non-toxic dose and anti-adenovirus type 7 activities of tested compounds on Hep2 cells determined by the end-point titration technique**.**

Tested compounds*	Viral reduction factor
6a	1
6b	1
6c	1
6d	10
7a	1
7b	1
7c	1
7d	10
10a	1
10b	10
10c	10
12a	10
12b	10

*Maximum non toxic dose for all the tested compounds = 0.1 mg/mL.

Table 3. Anti-rotavirus Wa strain activity of tested compounds on MA104 cells determined by the MTT method.

Tested compounds	CC_{50}, mg/mL	IC_{50}, mg/mL	Therapeutic index
6a	0.21 ± 0.041[a]	ND*	ND*
6b	0.20 ± 0.039	ND*	ND*
6c	0.21 ± 0.037	0.053 ± 0.009	4.21
6d	0.21 ± 0.027	0.056 ± 0.01	4.9
7a	0.21 ± 0.035	ND*	ND*
7b	0.22 ± 0.029	ND*	ND*
7c	0.22 ± 0.023	0.054 ± 0.005	4.68
7d	0.21 ± 0.025	0.051 ± 0.004	5.11
10a	0.20 ± 0.023	ND*	ND*
10b	0.21 ± 0.024	0.049 ± 0.007	5.11
10c	0.22 ± 0.024	0.047 ± 0.003	4.68
12a	0.21 ± 0.026	0.049 ± 0.004	5.11
12b	0.22 ± 0.029	0.047 ± 0.006	5.11

* Not detected. [a] Data represent mean values for at least three independent experiments (mean value ± S.D.).

Table 4. Anti-adenovirus type 7 strain activities of tested compounds on Hep2 cells determined by the MTT method.

Tested compounds	CC_{50}, mg/mL	IC_{50}, mg/mL	Therapeutic index
6a	0.18 ± 0.035[a]	ND*	ND*
6b	0.19 ± 0.033	ND*	ND*
6c	0.19 ± 0.028	ND*	ND*
6d	0.19 ± 0.039	0.062 ± 0.008	4.9
7a	0.18 ± 0.026	ND*	ND*
7b	0.19 ± 0.037	ND*	ND*
7c	0.19 ± 0.039	ND*	ND*
7d	0.19 ± 0.035	0.06 ± 0.009	5.11
10a	0.18 ± 0.031	ND*	ND*
10b	0.18 ± 0.029	0.061 ± 0.008	5.11
10c	0.19 ± 0.026	0.065 ± 0.008	4.68
12a	0.19 ± 0.027	0.065 ± 0.006	5.11
12b	0.19 ± 0.032	0.068 ± 0.007	5.11

*Not detected. [a] Data represent mean values for at least three independent experiments (mean value ± S.D.).

recorded with compounds **6c**, **6d**, **7c**, **7d**, **10b**, **10c**, **12a**, and **12b** against rotavirus Wa strain and compounds **6d**, **7d**, **10b**, **10c**, **12a**, and **12b** against adenovirus type 7 indicates high antiviral activity of the non toxic dose (0.1 mg/mL) (Tables 1 and 2).

Using MTT technique, the CC_{50} ranged from 0.2 to 0.22 mg/mL for tested compounds with MA104 cell line and ranged from 0.18 to 0.19 mg/mL for tested compounds with Hep-2 cell line. The IC_{50} for rotavirus Wa strain with tested compounds ranged from 0.047 to 0.056 mg/mL, while IC_{50} for adenovirus type 7 with tested compounds ranged from 0.06 to 0.068 mg/mL (Tables 3 and 4).

Regarding the structure activity relationship of the newly synthesized derivatives and according to Tables 3 and 4, the data revealed that derivatives **6c, d**, **7c, d**, **10b, c** and **12a, b** showed potent antiviral activity against both types of the tested viral strains; rotavirus Wa and adenovirus type 7, while the latter showed insensitivity towards derivatives **6c** and **7c**. It is worth mentioning that the attachment of pyrazole, pyrazolopyridazine and enaminone moieties to tetralin led to new derivatives of remarkable antiviral potency.

Substitution at N-1 of pyrazole or pyrazolopyridazine with a phenyl ring carrying the electron releasing group OCH_3 at its p-position as in **6d** and **7d** induced potent antiviral activity against both viral strains (IC_{50}: 0.056, 0.051 mg/mL and 0.062, 0.060 mg/mL, respectively), while the presence of electron withdrawing groups at p-position of the phenyl ring led to complete loss of the antiviral activity as exhibited by **6a–c** and **7a–c** compounds. In addition, rotavirus Wa strain showed high sensitivity towards the p-chloro derivatives **6c** and **7c** (IC_{50}: 0.053, 0.054 mg/mL, respectively).

The enaminone **10a** bearing p-flurophenyl substituent was devoid of any antiviral activity against both rotavirus Wa strain and adenovirus type 7, while the highest antiviral potency was observed by p-bromo derivative **10b** (IC_{50}: 0.049, 0.061 mg/mL), and 3,4-dimethoxyphenyl derivative **10c** against the tested strains (IC_{50}: 0.047, 0.065 mg/mL, respectively). Approximate equipotent activity was also obtained by the sulfa derivatives **12a, b** (IC_{50} of range 0.047–0.049 mg/mL against Wa and 0.061–0.068 mg/mL against adenovirus type 7).

The inhibition of viral adsorption to host cells, especially in the MTT assay, or interruption to viral life cycles are all possibilities in our screening of the antiviral activity of the tested compounds. The IC_{50} values of the tested compounds for adenovirus type 7 were higher than the IC_{50} values for the rotavirus Wa strain. This may be attributed to the nature of the viral genome since the adenovirus DNA genome may be more resistant than the rotavirus Wa strain RNA genome.

CONCLUSION

Some tested compounds (**6c**, **6d**, **7c**, **7d**, **10b**, **10c**, **12a**, and **12b**) of pyrazole, pyrazolo[3,4-*d*]pyridazine, secondary enaminones, and sulfonamides compounds showed antiviral effect against adenovirus type 7 and human rotavirus Wa strain, which may be promising compounds as anti-adenovirus 7 and human rotaviruses.

Acknowledgment

This work was supported by the Nationl Research Centre, Dokki, Cairo, Egypt. We are also grateful to Istituto di Chimica Biomolecolare Consiglio Nazionale delle Ricerche, Via Campi Flegrei, Pozzuoli, Naples, Italy for facilities and support. Special thanks to Prof. Dr. Guido Cimino, Dr. Margrita Givengi and Dr. Maria Letizia Ciavatta for their valuable help.

REFERENCES

1. Greenhill J.V.: Chem. Soc. Revs. 6, 277 (1977).
2. Bejan E., Haddou H.A., Daran J.C., Balavoine G.G.A.: Synthesis 8, 1012-1018 (1996).
3. Stanovnik B., Svete J.: Chem. Rev. 104, 2433 (2004).
4. Shaaban M.R., Saleh T.S., Farag A.M.: Heterocycles 71, 1765 (2007).
5. Tewari A.K., Mishra A.: Bioorg. Med. Chem. 9, 715 (2001).
6. Wiley R.H., Wiley P.: Pyrazolones Derivatives. John Wiley and Sons, New York 1964.
7. Reddy C.S., Rao L.S., Kumar G.R., Nagaraj A.: Chem. Pharm. Bull. 58, 1328 (2010).
8. Janus S.L., Magdif A.Z., Erik B.P., Claus N.: Monatsh. Chem. 130, 1167 (1999).
9. Wu L., Song B., Bhadury P., Yang S., Hu D., Jin L.: J Heterocycl. Chem. 48, 389 (2011).
10. Shih S., Chu T., Reddy G., Tseng S., Chen H., Tang W., Wu M. et al.: J. Biomed. Sci. 17, 13 (2010).
11. Park H.J., Lee K., Park S., Ahn B., Lee J.C., Cho H.Y., Lee K.I.: Bioorg. Med. Chem. Lett. 15, 3307 (2005).
12. Michon V., du Penhoat C.H., Tombret F., Gillardin J. M., Lepagez F., Berthon L.: Eur. J. Med. Chem. 30, 147 (1995).
13. Yildirim I., Özdemir N., Akçamur Y., Dinçer M., Andaç O.: Acta Cryst. 61, 256 (2005).
14. Bailey D.M., Hansen P.E., Hlavac A.G., Baizman E.R., Pearl J., Defelice A.F., Feigenson M.E.: J. Med. Chem. 28, 256 (1985).
15. Xia Y., Dong Z.W., Zhao B.X., Ge X., Meng N., Shin D.S., Miao J.Y.: Bioorg. Med. Chem. 15, 6893 (2007).
16. Lian S., Su H., Zhao B.X., Liu W.Y., Zheng L.W., Miao J.Y.: Bioorg. Med. Chem. 17, 7085 (2009).
17. Genin M.J., Biles C., Keiser B.J., Poppe S.M., Swaney S.M., Tarpley W.G., Yagi Y., Romero D.L.: J. Med. Chem. 43, 1034 (2000).
18. Tewari A.K., Mishra A.: Bioorg. Med. Chem. 9, 715 (2001).

19. Witherington J., Bordas V., Haigh D., Hickey D.M.B., Ife R.J., Rawlings A.D., Slingsby B.P. et al.: Bioorg. Med. Chem. Lett. 13, 1581 (2003).
20. Stevens K.L., Reno M.J., Alberti J.B., Price D.J., Kane-Carson L.S., Knick V.B., Shewchuk L.M. et al.: Bioorg. Med. Chem. Lett. 18, 5758 (2008).
21. Axarli I., Labrou N.E., Petrou C., Rassias N., Cordopatis P., Clonis Y.D.: Eur. J. Med. Chem. 44, 2009 (2009).
22. Ozawa Y., Sugi N.H., Nagasu T., Owa T., Watanabe T., Koyanagi N., Yoshino H. et al.: Eur. J. Cancer 37, 2275 (2001).
23. Dutta A.K., Fei X.S., Reith M.E.A.: Bioorg. Med. Chem. Lett. 12, 619 (2002).
24. Taddei P., Torreggiani A., Fini G.: Biopolymers 67, 289 (2002).
25. Hatori H., Sato B., Sato I., Shibata T., Tsurumi Y., Sakamoto K., Takase S. et al.: J. Antibiot. 57, 264 (2004).
26. Hamdy N.A., Gamal-Eldeen A.M.: Eur. J. Med. Chem. 44, 4547 (2009).
27. Song J.H., Slot A.J., Ryan R.W.J., Ross G.M.: Neuropharmacology 46, 984 (2004).
28. Carballal G., Videla C., Misirlian A., Requeijo P.V., Aguilar M.: BMC Pediatr. 2, 6 (2002).
29. Estes M., Kapikian A.: Rotaviruses, in Fields virology, 5th edn., Knipe D.M., Howley P.M., Griffin D.E., Lamb R.A., Martin M.A., Roizman B., Straus S.E. Eds., vol. 2, p. 1917, Lippincott, Williams and Wilkins, Philadelphia, PA 2007.
30. Hamdy N.A., Gamal-Eldeen A.M., Abdel-Aziz H.A., Fakhr I.M.I.: Eur. J. Med. Chem. 45, 463 (2010).
31. Abdel-Aziz H.A., Gamal-Eldeen A.M., Hamdy N. A., Fakhr I.M.I.: Arch. Pharm. 342, 230 (2009).
32. Abdel-Aziz H.A., Hamdy N.A., Gamal-Eldeen A.M., Fakhr I.M.I.: Z. Naturforsch. 66c, 7 (2011).
33. Allinger N.L., Jones E.S.: J. Org. Chem. 27, 70 (1962).
34. (a) Dieckmann W., Platz O.: Ber. Dtsch. Chem. Ges. 38, 2989 (1906). (b) Eweiss N.F., Abdelhamid A.O.: J. Heterocycl. Chem. 17, 1713 (1980).
35. Simões C., Amoros M., Girre L.: Phytother. Res. 21, 317 (1999).
36. Walum E., Strenberg K., Jenssen D.: Understanding Cell Toxicology: Principles and Pratice, p. 97, Ellis Howood, NewYork 1990.
37. Mosmann T.: J, Immunol. Methods 65, 55 (1983).
38. Vlietinck A.J., Van Hoof L., Totté J., Lasure A., Berghe D.V., Rwangabo P.C., Mvukiyumwami J.: J. Ethnopharmacol. 46, 31 (2002).
39. Shaaban M.R., Salah T.S., Osman F. H., Farag A.M.: J. Heterocycl. Chem. 44, 177 (2007).
40. Almazroa S., Elnagdi M.H., Salah El-Din A.M.: J. Heterocycl. Chem. 41, 267 (2004).
41. Caramella P., Grunanger P.: in 1,3-dipolar cycloaddition chemistry, Padwa, A. Ed., Vol 1, p. 292, Wiley and Sons, New York 1984.
42. Easton C.J., Hughes C.M.M., Sevage G.P., Simpson G.W.: Heterocycl. Chem. 60, 261 (1994).
43. Demirbas N., Karaoglu S.A., Demirbas A., Sancak K.: Eur. J. Med. Chem. 39, 793 (2004).
44. Martins M.A.P., Peres R.L., Fiss G.F., Dimer F.A., Mayer R., Frizzo C.P., Marzari M.R.B. et al.: J. Braz. Chem. Soc. 18, 1486 (2007).
45. Potin D., Dumas F., Angelo J.: J. Am. Chem. Soc. 112, 3483 (1999).

Received: 24. 10. 2011