SYNTHESIS AND ANTIOXIDANT ACTIVITY OF SOME BENZIMIDAZOLE AND INDOLE DERIVATIVES CONTAINING [1, 2, 4]TRIAZOLE RING.

BY

Mohamed M. Said [1], Nagat Ghareb[1], Pierre Hanna[2] and Adel A. El-Gendy [3]

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[1]Organic Chemistry Department, Faculty of Pharmacy, Suez Canal University, Egypt;

[2]Pharmaceutics Department, Faculty of Pharmacy, Suez Canal University, Egypt.

[3]Organic Chemistry Department, Faculty of Pharmacy, Misr International University, Egypt;

ABSTRACT

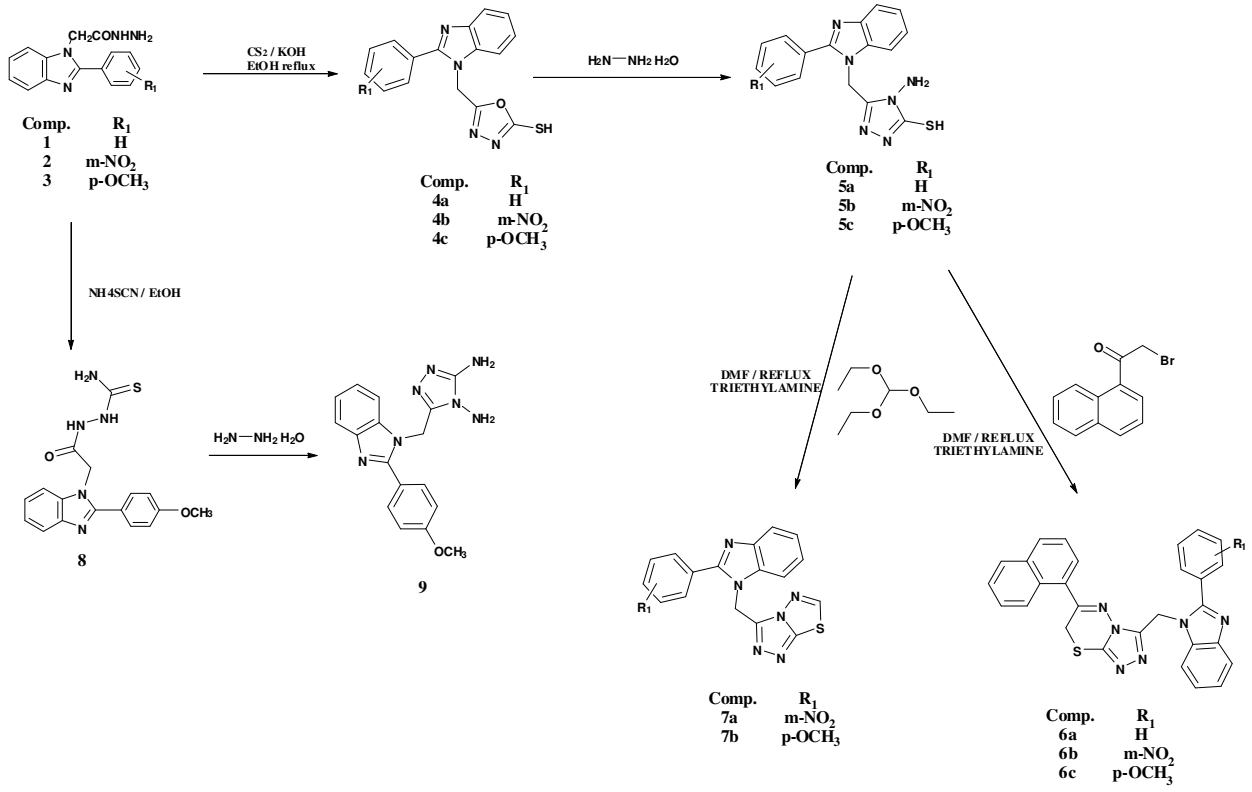
*The oxadiazoles **4a-c** were converted to the corresponding 4-amino-5-((2-subsituted phenyl-1H-benzo[d]imidazol-1-yl) methyl)-4H-1, 2, 4-triazole-3-thiols **5a-c** by hydrazinolysis. Cyclocondensation of **5a-c** with 2-bromo-1-(naphthalen-1-yl)ethanone and ethyl orthoformate led to 6-(naphthalen-1-yl)-3-((2-phenyl-1H-benzo[d]imidazol-1-yl)methyl)-7H-[1,2,4]triazolo[3,4 b][1,3,4]thiadiazines **6a-c** and 3-((2-subsitutedphenyl-1H-benzo[d]imidazol-1-yl)methyl)-[1,2,4]triazolo[3,4-b]-[1,3, 4]thiadiazoles **7a-b** respectively. Condensation of 2-(2-(2-(4-methoxyphenyl)-1H-benzo[d]imidazol-1-yl) acetyl) hydrazinecarbothioamide **8** with hydrazine afforded 5-((2-(4-methoxyphenyl)-1H-benzo[d]imidazol-1-yl) methyl)-4H-1,2,4-triazole-3,4-diamine **9**. Ring closure of oxadiazole **11** with an excess of hydrazine hydrate afforded 4-amino-5-(5-fluoro-1H-indol-2-yl)-4H-1, 2, 4-triazole-3-thiol **12** whose reaction with 2-bromo-1-(naphthalen-1-yl)ethanone and ethyl orthoformate in presence of DMF led to thiadiazine **13** and 3-(5-fluoro-1H-indol-2-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole **14** respectively. The antioxidant activities were tested in vitro using DPPH radical scavenging assay.*

INTRODUCTION

Benzimidazoles and their attached other heterocycles such as oxadiazoles, triazoles and thiadiazoles have been reported to possess antibacterial (Ferandes and Sonar, 1986), antifungal (Singh *et al*., 1981) and antioxidant activities (Canan *et al*., 2008). Based on these findings, it was decided to incorporate oxadiazoles, thiadiazoles and triazoles in the benzimidazole ring to yield compounds with promising antioxidant activity. On the other hand, indole derivatives bearing five membered heterocycles such as oxazoles, oxadiazoles, triazoles and thiadiazoles have been reported to possess anti-inflammatory (Mullican *et al*., 1993 and Boschelli *et al*., 1993), antiviral (Witkowski *et al*., 1973) and antimicrobial (Shams El-Din and Hazzaa, 1974) and antioxidant (Kaneko *et al*., 2000) properties. based on these findings, synthesis of some new indole heterocycles were carried out and evaluated for antioxidant activity.

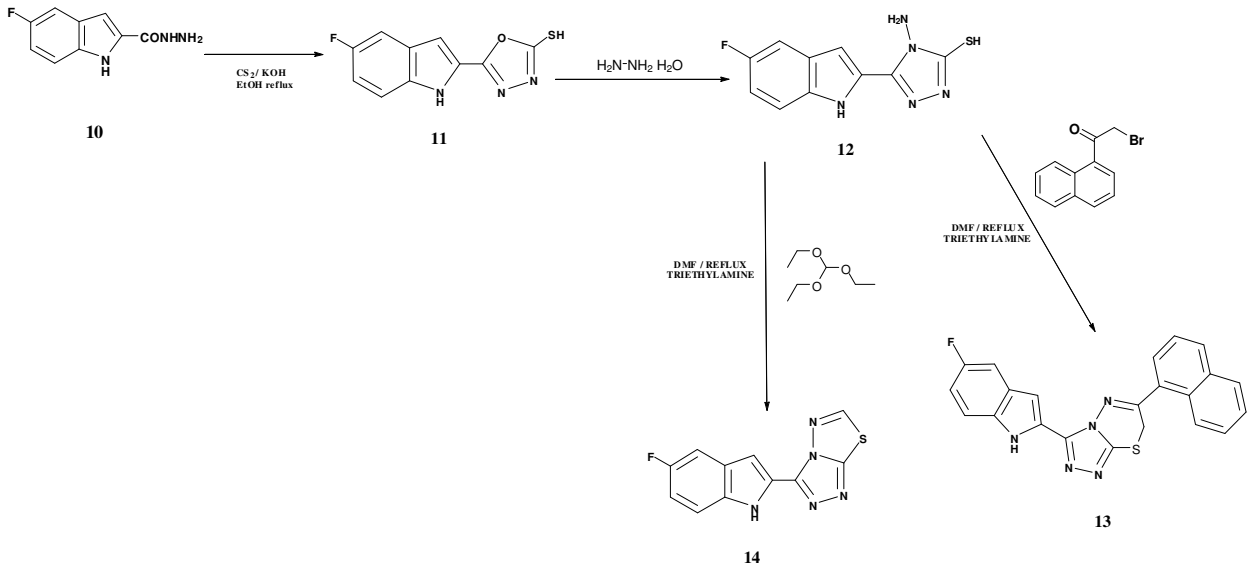
RESULTS AND DISCUSSION

The reaction of 2[2-(substitutedphenyl)-1H-benzo[d]imidazol-1-yl]aceto-hydrazides 1-3 with carbon disulphide in alkaline medium afforded, after acidic treatment, 5-((2-subsituted phenyl-1H-benzo[d]imidazol-1-yl)methyl)-1,3,4-oxadiazole-2-thiols 4a-c (Young and Wood, 1955 and Kassem and El-masry, 1995). The oxadiazoles 4a-c could be converted into the corresponding 4-amino-5-((2-subsituted phenyl-1H-benzo[d]imidazol-1-yl) methyl)-4H-1, 2, 4-triazole-3-thiols 5a-c by hydrazinolysis (El-masry *et al*., 2000). The ^{1}H NMR spectrum of compounds 5a-c showed the two characteristic singlets of the NH_2 and SH protons at δ 5.61 and 13.62, respectively.Cyclocondensation of 5a-c with 2-bromo-1-(naphthalen-1-yl)ethanone and ethyl orthoformate in presence of dimethyl formamide led to 6-(naphthalen-1-yl)-3-((2-phenyl-1H-benzo[d]imidazol-1-yl)methyl)-7H-[1,2,4]triazo-lo[3,4-b][1,3,4]thiadiazines 6a-c and 3-((2-subsitutedphenyl-1H-benzo[d]imidazol-1-yl)methyl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazoles 7a-b respectively. Reaction of 3 with ammonium thiocyanate in refluxing ethanol containing catalytic amounts of HCl for 10 h gave 2-(2-(2-(4-methoxyphenyl)-1H-benzo[d]imidazol-1-yl)acetyl)hydra-zinecarbothioamide 8 (Koparir *et al*., 2005). Condensation of 8 with hydrazine afforded 5-((2-(4-methoxyphenyl)-1H-benzo[d]imidazol-1-yl)methyl)-4H-1,2,4-tria-zole-3,4-diamine 9 (Misra *et al*., 1996). (Scheme 1)



Scheme (1): The synthesis of benzimdazole heterocycles

The reaction of 5-fluoro-1H-indole-2-carbohydrazide 10 with carbon disulphide in alkaline medium afforded, after acidic treatment, 5-(5-fluoro-1H-indol-2-yl)-1,3,4-oxadiazole-2-thiol 11 (Misra *et al*., 1996) . Ring closure of oxadiazole 11 with an excess of hydrazine hydrate afforded 4-amino-5-(5-fluoro-1H-indol-2-yl)-4H-1, 2, 4-triazole-3-thiol 12 in 78% yield upon heating for 10 h (Misra *et al*., 1996). Its ^{1}H NMR spectrum showed the two characteristic singlet of the NH_2 and SH protons at δ 6.36 and 12.62, respectively. cyclocondensation of 12 with 2-bromo-1-(naphthalen-1-yl)ethanone and ethyl orthoformate in presence of dimethyl formamide led to thiadiazine 13 and 3-(5-fluoro-1H-indol-2-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole 14 respectively. The IR and ^{1}H NMR spectra of 13 and 14 confirmed the success of the cyclization by the disappearance of the signals corresponding to the NH_2 and SH protons. (Scheme 2)



Scheme (2): Reactions of 5-fluoro-1H-indole-2-carbohydrazide

Antioxidant test:

Compounds 4a-c, 5a-c, 6a-c, 7a-b, 9, 11, 12, 13 and 14 were evaluated for their antioxidant activity by TLC-based 1,1- diphenyl-2-picrylhydrazyl radical (DPPH) autographic chemical assay (Takamatsu *et al*., 2003).

Method

DPPH* (1, 1-diphenyl-2-picrylhydrazyl radical) is a stable free radical that can accept an electron or hydrogen radical to become a stable diamagnetic molecule. The radical scavenging potential of the compounds is determined by formation of its reduced form, l,l-diphenyI-2-picrylhydrazine (DPPH), which is yellow in color. Synthesized compounds were dissolved in methanol at a concentration of 0.15 mg/ml. Total volume of 4µl of each compound was applied in the form of a spot (4-5 mm in diameter) on silica gel GF plates. A similar amount of vitamin C in methanol was

used as positive antioxidant control. The radical-scavenging effects of the synthesized compounds were detected on the TLC plate using a spray reagent composed of a 0.02 % (w/v) methanolic solution of 1,1- diphenyl-2-picrylhydrazyl radical (DPPH). The plate was observed 30 min after spraying. Active compounds were observed as yellow spots against a purple background. Relative radical-scavenging activity was assigned as "strong" (compounds that produce an intense bright yellow zone), "medium" (compounds that produce a clear yellow spot), "weak" (compounds that produce a weakly visible yellow spot), or "not active" (compounds that produce no sign of any yellow spot). Vitamin C was taken as positive antioxidant control which produced an intense bright yellow zone.

Anti-oxidant evaluation of synthesized compounds revealed that compounds 4a-c, 5a-c, 11 and 12 possesses "strong" anti-oxidant activity while compounds 6a-c, 7a-b, 9, 13 and14 have "medium" anti-oxidant activity.

EXPERIMENTAL

General

Melting points were measured in open capillary tubes using Stuart melting point apparatus SMP10 and are uncorrected. Infrared (IR) spectra were recorded using KBr discs on a Shimadzu Spectrophotometer (υmax in cm^{-1}). Proton Magnetic Resonance (^{1}H-NMR) spectra were recorded on Mercury–300 BB (NMR300) spectrometer (300MHz). Chemical shifts are reported in δ values (parts per million, ppm) relative to tetramethylsilane (TMS) as internal standard and coupling constant values are given in Hz.. Electron impact mass spectra (EI-MS) were recorded on DI Analysis Shimadzu QP-2010 Plus mass spectrometer. IR, ^{1}H-NMR, EI-MS and Elemental analyses were performed in the Microanalytical center, Cairo University, Egypt. Reactions were monitored by thin layer chromatography (TLC) on Merck silica gel 60F254 and visualized with UV light.

General procedure for the preparation of 2[2-(substitutedphenyl)-1H-benzo[d]imidazol-1-yl] acetohydrazides **1-3** (Canan *et al*., 2008)

Hydrazine hydrate (4 ml, 80%) and corresponding ethyl 2[2-(substitutedphenyl)-1H-benzo[d] imidazol-1-yl]-acetate**s** (1.5 mmol) in ethanol (20 ml) were refluxed for 4 h. The reaction mixture was cooled and poured into water. The crude product was filtered off and recrystallized from ethanol to give the desired hydrazides 1-3

2-(2-Phenyl-1H-benzo[d]imidazol-1-yl) acetohydrazide **1:** mp 210-213˚C, lit. Jerchel *et al*., 1954) mp 203-204˚C (yield 85%). IR (cm^{-1}): 1541(C=N), 1656(C=O), 3194(NH_2) 3302(NH). Mass spectrum: m/z(%): 266(M^+, 207(100%)..

2-(2-(3-Nitrophenyl)-1H-benzo[d]imidazol-1 yl) acetohydrazide 2: mp 220-223˚C, (yield 90%). IR (cm^{-1}): 1349(N-O), 1537(C=N), 1697(C=O), 3199(NH_2), 3323(NH). Mass spectrum: m/z(%): 311(M^+, 100%), 296(4.06%), 280(7.82%), 266(1.90%), 252(69.06%), 235(47.63%), 222(13.61%), 206(86.70%), 193(17.21%), 179(9.82%), 167(5.81%), 149(13.14%), 129(8.81%), 118(3.25%), 103 (12.09%), 85(6.28%), 77(64.89%), 63(7.26%), 51(30.93%).

2-(2-(4-Methoxyphenyl)-1H-benzo[d]imidazol-1-yl) acetohydrazide 3: mp 180-183˚C, (yield 88%). IR (cm^{-1}): 1246(C-O-C), 1611(C=N), 1693(C=O), 3229(NH_2), 3333(NH). Mass spectrum: m/z(%): 296(M^+, 75.43%), 281(1.01%), 265(12.51%), 237(100%), 222(33.79%), 206(10.56%), 194(21.35%), 167(2.47%), 148(1.32%), 129(6.81%), 119(0.62%), 103(4.83%), 90(3.47%), 77(23.54%), 63(2.92%), 51(10.56%).

General procedure for the preparation of 5-((2-substitutedphenyl-1H-benzo[d]imidazol-1-yl)methyl)-1,3,4-oxadiazole-2-thiols **4a-c**

A solution of KOH (15 mmol), 2[2-(substitutedphenyl)-1H-benzo[d]imidazol-1yl] acetohydrazides 1-3 (10 mmol) and CS_2 (15 mmol) in absolute ethanol (100 ml) was refluxed for 10 h. Then it was cooled to room temperature and diluted with dry ether (100 ml). The precipitate thus obtained was filtered and washed with ether and dried. A suspension of this solid (10 mmol) in aqueous KOH (20 mmol) was refluxed till the evolution of H_2S ceased. Dilution with water (100 ml) and acidification with HCl yielded solid, which was filtered, washed with water and recrystallized from ethanol.

5-((2-Phenyl-1H-benzo[d]imidazol-1-yl)methyl)-1,3,4-oxadiazole-2-thiol 4a: mp 255-257˚C, (yield 55%). IR (cm^{-1}): 1150(C-O-C), 1614(C=N), 2650(SH). Mass spectrum: m/z(%): 308(M^+, 0%), 292(0.20%), 266(0.84%), 248(0.18%), 232(0.54%), 219(0.99%), 207(4.45%), 192(1.81%), 178(0.42%), 160(1.09%), 149(0.73%), 128(1.45%), 103(0.72%), 76(100%), 55(14.41%). ^{1}H-NMR (DMSO, 300 MHz): δ(ppm) = 2.30(s, 1H, SH), 5.35(s, 2H, CH_2), 7.06-7.98(m, 9H, Ar-H). Anal.Calcd. for $C_{16}H_{12}N_4OS$: C, 62.32; H, 3.92; N, 18.17. Found: C, 62.13; H, 3.65; N, 18.14.

5-((2-(3-Nitrophenyl)-1H-benzo[d]imidazol-1-yl)methyl)-1,3,4-oxadiazole-2-thiol 4b Mp 230-233˚C, (yield 70%). Mass spectrum: m/z(%): 351(M^+-2, 4.37%), 337(2.51%), 296(6.40%), 278(5.12%), 252(20.57%), 239(66.97%), 224(7.26%), 206(36.81%), 193(56.58%), 178(22.91%), 160(17.06%), 143(33.22%), 129(16.98%), 120(19.89%), 102(17.41%), 90(23.85%), 76(62.10%), 64(100%), 55(63.50%). Anal.Calcd. for $C_{16}H_{11}N_5O_3S$: C, 54.38; H, 3.14; N, 19.82. Found: C, 54.13; H, 3.05; N, 19.80.

5-((2-(4-Methoxyphenyl)-1H-benzo[d]imidazol-1-yl)methyl)-1,3,4-oxadiazole-2-thiol **4c:** mp 227-230˚C, (yield 85%). IR (cm^{-1}): 1262(C-O-C), 1606(C=N), 2330(SH). Mass spectrum: m/z(%): 338(M^+, 100%), 322(1.55%), 306(1.13%), 280(12.88%), 262(7.43%), 237(52.40%), 223(24.71%), 209(9.60%), 194(16.14%), 181(7.09%), 166(2.07%), 147(7.59%), 133(13.87%), 119(4.22%), 103(8.29%), 90(10.92%), 77(21.97%), 63(7.00%), 51(9.78%). ^{1}H-NMR (DMSO, 300 MHz): δ(ppm) = 3.88(s, 3H, OCH_3), 6.06(s, 2H, CH_2), 7.22-8.04(m, 8H, Ar-H), 9.33(s, 1H, SH). Anal.Calcd. for $C_{17}H_{14}N_4O_2S$: C, 60.34; H, 4.17; N, 16.56. Found: C, 60.21; H, 4.05; N, 16.36.

General procedure for the preparation of 4-amino-5-((2-substituted phenyl-1H-benzo[d]imidazol-1-yl)methyl)-4H-1,2,4-triazole-3-thiols **5a-c**

A suspension of 5-((2-substituted phenyl-1H-benzo[d]imidazol-1-yl)methyl)-1,3,4-oxadiazole-2-thiols 4a-c (10 mmol) in hydrazine hydrate (20 mmol, 99%) was refluxed for 10 h,cooled. diluted with water and acidified with HCl till a white solid separated out. This was filtered, washed with water and recrystallized from ethanol.

4-Amino-5-((2-phenyl-1H-benzo[d]imidazol-1-yl)methyl)-4H-1,2,4-triazole-3-thiol 5a

Mp 235-237˚C, (yield 72%). IR (cm^{-1}): 1615(C=N), 2600(SH), 3252, 3300(NH_2). Mass spectrum: m/z(%): 322(M^+, 0.39%), 309(0.86%), 295(1.02%), 281(1.09%), 267(1.21%), 253(1.39%), 239(1.59%), 225(1.71%), 211(1.95%), 197(2.24%), 183(2.69%), 169(3.14%), 155(3.81%), 141(4.95%), 127(6.48%), 113(8.95%), 99(13.94%), 85(41.26%), 71(61.63%), 57(100%). ^{1}H-NMR (DMSO, 300 MHz): δ(ppm) = 5.56(s, 2H, CH_2), 5.61(br.s, 2H, NH_2), 7.25-7.80(m, 9H, Ar-H), 13.62(s, 1H, SH). Anal.Calcd. for $C_{16}H_{14}N_6S$: C, 59.61; H, 4.38; N, 26.07. Found: C, 59.58; H, 4.11; N, 25.80.

4-Amino-5-((2-(3-nitrophenyl)-1H-benzo[d]imidazol-1-yl)methyl)-4H-1,2,4-triazole-3-thiol 5b: mp 225-227˚C, (yield 81%). IR (cm^{-1}): 1458(N-O), 1615(C=N), 2362(SH), 3241(NH_2). Mass spectrum: m/z(%): 367(M^+, 0%), 337(98.98%), 322(21.06%), 305(3.69%), 291(3.23%), 262(2.49%), 249(32.67%), 234(12.54%), 209(100%), 182(22.02%), 156(3.85%), 143(3.79%), 129(7.69%), 118(36.53%), 104(9.89%), 91(17.69%), 77(21.71%), 64(28.04%), 51(13.56%). ^{1}H-NMR (DMSO, 300 MHz): δ(ppm) = 5.55(s, 2H, CH_2), 5.63(br.s, 2H, NH_2), 6.71-7.46(m, 8H, Ar-H), 13.60(s, 1H, SH). Anal.Calcd. for $C_{16}H_{13}N_7O_2S$: C, 52.31; H, 3.57; N, 26.69. Found: C, 52.13; H, 3.55; N, 26.54.

4-Amino-5-((2-(4-methoxyphenyl)-1H-benzo[d]imidazol-1-yl)methyl)-4H-1,2,4-triazole-3-thiol 5c: mp 240-243˚C, (yield 60%). ^{1}H-NMR (DMSO, 300 MHz): δ(ppm) = 3.79(s, 3H, OCH_3), 5.20(s, 2H, CH_2), 5.60(br.s, 2H, NH_2), 7.18-7.89(m, 8H, Ar-H), 11.98(s, 1H, SH). Anal.Calcd. for $C_{17}H_{16}N_6OS$: C, 57.94; H, 4.58; N, 23.85. Found: C, 57.80; H, 4.54; N, 23.81.

General procedure for the preparation of 6-(naphthalen-1-yl)-3-((2-phenyl-1H-benzo[d]imidazol-1-yl)methyl)-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazines **6a-c**

4-Amino-5-((2-subsitutedphenyl-1H-benzo[d]imidazol-1-yl)methyl)-4H-1,2,4-triazole -3-thiols **5a-c** (2 mmol) and 2-bromo-1-(naphthalen-1-yl)ethanone (1 mmol) were refluxed in dimethylformamide (DMF) (10 ml) in the presence of triethylamine (one drop) for 10 h. The reaction mixture was cooled and poured into crushed ice. The crude product was filtered off and recrystallized from DMF / ethanol mixture.

6-(Naphthalen-1-yl)-3-((2-phenyl-1H-benzo[d]imidazol-1-yl)methyl)-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine 6a: mp 166-163˚C, Mass spectrum: m/z(%): 472(M^+, 1.16%), 400(7.11%), 386(15.94%), 360(7.71%), 347(8.02%), 308(6.66%), 284(9.25%), 259(2.01%), 233(1.03%), 207(15.15%), 193(14.03%), 179(2.84%), 153(98.10%), 126(17.36%), 116(4.59%), 105(12.27%), 89(2.22%), 76(100%), 50(10.22%). ^{1}H-NMR (DMSO, 300 MHz): δ(ppm) = 4.65-4.75(dd, 2H, CH_2 thiadiazine), 5.88(s, 2H, CH_2), 7.04-8.89(m, 16H, Ar-H). Anal.Calcd. for $C_{28}H_{20}N_6S$: C, 71.16; H, 4.27; N, 17.78. Found: C, 70.92; H, 4.24; N, 17.36.

6-(Naphthalen-1-yl)-3-((2-(3-nitrophenyl)-1H-benzo[d]imidazol-1-yl)methyl)-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine 6b: mp 200-203˚C, Mass spectrum: m/z(%): 517(M^+, 5.16%), 448(5.01%), 434(5.94%), 421(5.94%), 407(6.09%), 389(5.55%), 352(0.39%), 329(0.05%), 306(1.03%), 284(5.55%), 256(4.03%), 242(5.84%), 228(7.81%), 209(30.70%), 185(14.83%), 172(10.51%), 155(95.04%), 127(77.36%), 118(14.59%), 106(10.27%), 88(18.22%), 73(100%), 63(21.76%), 50(10.22%). Anal.Calcd. for $C_{28}H_{19}N_7O_2S$: C, 64.98; H, 3.70; N, 18.94. Found: C, 64.87; H, 3.55; N, 18.86.

3-((2-(4-Methoxyphenyl)-1H-benzo[d]imidazol-1-yl)methyl)-6-(naphthalen-1-yl)-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine 6c: mp 130-133˚C, Mass spectrum: m/z(%): 502(M^+, 11.12%), 430(15.01%), 416(3.94%), 390(2.23%), 377(16.09%), 338(8.81%), 314(2.39%), 289(11.02%), 263(8.03%), 237(25.55%), 223(20.03%), 209(19.23%), 194(7.81%), 178(30.70%), 156(90.24%), 130(17.36%), 112(19.59%), 88(20.69%), 76(100%), 63(30.36%), 50(19.22%). Anal.Calcd. for $C_{29}H_{22}N_6OS$: C, 69.30; H, 4.41; N, 16.72. Found: C, 69.16; H, 4.26; N, 16.67.

General procedure for the preparation of 3-((2-substitutedphenyl-1H-benzo[d]imidazol-1-yl)methyl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazoles **7a-b**

A mixture of 4-amino-5-((2-(subsituted phenyl)-1H-benzo[d]imidazol-1-yl)methyl)-4H-1,2,4-triazole-3-thiols 5b-c (1 mmol), N,N dimethylformamide (5 ml), and ethyl orthoformate (2 mmol) was refluxed for 25 h. Solvent was removed and the residue recrystallized from DMF / ethanol mixture.

3-((2-(3-Nitrophenyl)-1H-benzo[d]imidazol-1-yl)methyl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole 7a: mp 220-223˚C, (yield 70%). Mass spectrum: m/z(%): 377/378/379(M^+/M^++1/M^++2, 18.45%/33.40%/9.91%), 350(20.47%), 335(18.37%), 303(3.07%), 278(4.33%), 251(100%), 237(10.55%), 222(47.45%), 206(16.39%), 195(16.27%), 167(6.07%), 142(31.78%), 125(16.62%), 111(32%), 97(36.47%), 69(77.69%), 57(74.47%). ^{1}H-NMR (DMSO, 300 MHz): δ(ppm) = 5.29(s, 2H, CH_2), 6.99(s, 1H, CH thiadiazole), 7.18-7.41(m, 8H, Ar-H).Anal.Calcd. for $C_{17}H_{11}N_7O_2S$: C, 54.11; H, 2.94; N, 25.98. Found: C, 54.05; H, 2.87; N, 25.82.

3-((2-(4-Methoxyphenyl)-1H-benzo[d]imidazol-1-yl)methyl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole 7b: mp 130-132˚C, (yield 77%). Mass spectrum: m/z(%): 362/363/364(M^+/M^++1/M^++2, 14.45%/27.40%/7.71%), 335(10.17%), 321(15.47%), 289(5.37%), 263(8.33%), 237(100%), 223(18.55%), 209(57.45%), 194(36.49%), 178(19.97%), 153(12.07%), 127(62.78%), 102(6.62%), 69(17.69%), 57(24.47%) ^{1}H-NMR (DMSO, 300 MHz): δ(ppm) = 3.68(s, 3H, OCH_3), 5.20(s, 2H, CH_2), 6.88(s, 1H, CH thiadiazole), 7.18-7.41(m, 8H, Ar-H). Anal.Calcd. for $C_{18}H_{14}N_6OS$: C, 59.65; H, 3.89; N, 23.19. Found: C, 59.48; H, 3.82; N, 23.01.

Preparation of 2-(2-(2-(4-methoxyphenyl)-1H-benzo[d]imidazol-1-yl)acetyl) hydrazine carbothioamide **8**

An equimolar quantity of 2-(2-(4-methoxyphenyl)-1H-benzo[d]imidazol-1-yl)acetohydrazide 3 (0.29 g, 1 mmol) ammonium thiocyanate (0.076 g, 1 mmol) and hydrochloric acid (3 ml) in absolute ethanol (30 ml) were refluxed for 10 h. the white solid that appeared on cooling was filtered and the excess solvent was removed by evaporation. The residue was recrystallized from ethanol.

Mp 255-256˚C, (yield 60%). IR (cm^{-1}): 1266(C-O-C), 1467(C=N), 1604(C=S), 1717(C=O), 3089-3100(NH_2), 3380(NH). Mass spectrum: m/z(%): 355(M^+, 0%), 336(0.06%), 322(0.10%), 308(0.22%), 296(75.03%), 281(0.65%), 265(12.29%), 237(100%), 222(34.23%), 206(11.25%), 194(23.76%), 167(2.41%), 140(1.47%), 129(7.79%), 119(5.50%), 103(5.72%), 90(4.31%), 77(31.31%), 63(3.57%), 51(13.36%).

Preparation of 5-((2-(4-methoxyphenyl)-1H-benzo[d]imidazol-1-yl)methyl)-4H-1,2,4-triazole-3,4-diamine **9**

A suspension of 2-(2-(2-(4-methoxyphenyl)-1H-benzo[d]imidazol-1-yl)acetyl)

hydrazinecarbothioamide 8 (1 mmol) in hydrazine hydrate (2 mmol, 99%) was refluxed for 5 h. It was then diluted with water and acidified with HCl, and a white solid separated out. This was filtered, washed with water and recrystallized from ethanol.

Mp 195-196˚C, (yield 65%). IR (cm^{-1}): 1588(C=N), 3152-3175(NH_2). Mass spectrum: m/z(%): 337(M^++2, 4.53%), 322(0.38%), 308(0.65%), 296(71.38%), 282(8.14%), 265(11.55%), 237(100%), 222(34.86%), 206(12.34%), 194(25.26%), 167(3.94%), 140(2.35%), 129(11.05%), 119(8.19%), 103(8.59%), 90(6.94%), 77(44.88%), 63(6.66%), 51(23.36%). ^{1}H-NMR (DMSO, 300 MHz): δ(ppm) = 3.80(s, 3H, OCH_3), 5.22(s, 2H, CH_2), 6.5(br.s, 4H, $(NH_2)_2$), 7.18-7.41(m, 8H, Ar-H). Anal.Calcd. for $C_{17}H_{17}N_7O$: C, 60.88; H, 5.11; N, 29.24. Found: C, 60.81; H, 5.05; N, 29.13.

5-(5-Fluoro-1H-indol-2-yl)-1, 3, 4-oxadiazole-2-thiol **11**

A solution of KOH (15 mmol), 5-fluoro-1H-indole-2-carbohydrazide **10** (10 mmol) and CS_2 (15 mmol) in absolute ethanol (100 ml) was refluxed for 6 h. Then it was cooled to room temperature and diluted with dry ether (100 ml). The precipitate thus obtained was filtered and washed with ether and dried. A suspension of this solid (10 mmol) in aqueous KOH (20 mmol) was again refluxed until the evolution of H_2S ceased. Dilution with water (100 ml) and acidification with HCl yielded solid, which was filtered, washed with water and recrystallized from ethanol.

Mp 240-243˚C, (yield 70%). IR (cm^{-1}): 749(C-F), 1610(C=N), 2540(SH), 3120(NH). Mass spectrum: m/z(%): 235/236/237(M^+/M^++1/M^++2, 65.84%/8.93%/4.05%), 222(0.98%), 208(0.95%), 192(1.47%), 175(10.45%), 162(100%), 148(9.96%), 134(14.27%), 121(27.11%), 107(32.37%), 87(18.98%), 57(14.45%). ^{1}H-NMR (DMSO, 300 MHz): δ(ppm) = 2.78(s, 1H, SH), 6.68(s, 1H, C_3-indole), 6.60-7.01(m, 3H, Ar-H), 10.23(s, 1H, NH). Anal.Calcd. for $C_{10}H_6FN_3OS$: C, 51.06; H, 2.57; N, 17.86. Found: C, 50.92; H, 2.36; N, 17.83.

4-Amino-5-(5-fluoro-1H-indol-2-yl)-4H-1, 2, 4-triazole-3-thiol **12**

A suspension of 5-(5-fluoro-1H-indol-2-yl)-1, 3, 4-oxadiazole-2-thiol 11 (10 mmol) in hydrazine hydrate (3 ml, 99%) was refluxed for 10 h. It was then diluted with water and acidified with HCl, a white solid separated out. This was filtered, washed with water and recrystallized from ethanol.

Mp 291-293˚C, (yield 78%). IR (cm^{-1}): 756(C-F), 1599(C=N), 2320(SH), 3120-3263(NH/NH_2). Mass spectrum: m/z(%): 249(M^+, 2.39%), 233(12.86%), 219(100%), 186(21.09%), 160(21.21%), 134(13.39%), 119(16.59%), 94(8.71%), 70(10.95%), 57(52.24%). ^{1}H-NMR (DMSO, 300 MHz): δ(ppm) = 6.36(s, 2H, NH_2), 7.89(s, 1H, C_3-indole), 6.60-7.20(m, 3H, Ar-H), 10.02(s, 1H, NH), 12.62(s, 1H, SH). Anal.Calcd. for $C_{10}H_8FN_5S$: C, 48.18; H, 3.23; N, 28.10. Found: C, 48.06; H, 3.15; N, 28.01.

3-(5-fluoro-1H-indol-2-yl)-6-(naphthalen-1-yl)-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine **13**

4-Amino-5-(5-fluoro-1H-indol-2-yl)-4H-1,2,4-triazole-3-thiol 12 (1 mmol) and 2-bromo-1-(naphthalen-1-yl)ethanone (1 mmol) were refluxed in N,N-dimethylformamide (10 ml) in the presence of triethylamine (one drop) for 15 h. The reaction mixture was cooled and poured into crushed ice. The crude product was filtered off and recrystallized from DMF / ethanol mixture.

Mp >300˚C, (yield 72%). IR (cm^{-1}): 756(C-F), 1600(C=N), 3352(NH). ^{1}H-NMR (DMSO, 300 MHz): δ(ppm) = 4.65-4.75(dd, 2H, CH_2 thiadiazine),6.70-8.60(m, 10H, Ar-H), 7.86(s, 1H, C_3-indole), 10.23(s, 1H, NH). Anal.Calcd. for $C_{22}H_{14}FN_{5S}$ C, 66.15; H, 3.53; N, 17.53 Found: C, 65.71; H, 3.05; N, 18.14.

3-(5-Fluoro-1H-indol-2-yl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole **14**

A mixture of 4-amino-5-(5-fluoro-1H-indol-2-yl)-4H-1, 2, 4-triazole-3-thiol 12 (1 mmol), N,N dimethylformamide (5 mL), and ethyl orthoformate (2 mmol) was refluxed for 15 h. Solvent was removed and the residue recrystallized from DMF / ethanol mixture.

Mp >300˚C, (yield 71%). IR (cm^{-1}): 736(C-F), 1586(C=N), 3269(NH). Mass spectrum: m/z(%): 259(M^+, 27.40%), 227(15.17%), 214(15.47%), 200(51.37%), 186(9.33%), 160(31.1%), 134(18.55%), 119(27.45%), 94(36.49%), 70(19.97%), 57(100%). ^{1}H-NMR (DMSO, 300 MHz): δ(ppm) = 6.78-7.60(m, 3H, Ar-H), 7.52(s, 1H, thiadiazole), 7.93(s, 1H, C_3-indole), 9.89(s, 1H, NH). Anal.Calcd. for $C_{11}H_6FN_5S$: C, 50.96; H, 2.33; N, 27.01. Found: C, 50.92; H, 2.20; N, 26.92.

REFERENCES

Ferandes, P.S.; Sonar, T.M. (1986): *J. Indian Chem. Soc.* LXlII, 427-429.

Singh, S.; Yadav, L.D.S.; Singh, H. (1981): *Indian. J. Chem.* 20B, 518-520.

Canan, K.; Gülgün, A.S.; Özbey, F.B.; Melek, T.C.; Benay, C. (2008): *Bioorganic & Medicinal Chemistry* 16, 4294–4303.

Mullican, M.D.; Wilson, M.W.; Connor, D.T.; Kostlan, C.R.; Shrier, D.J.; Dyer, R.D. (1993): J. Med. Chem. 36, 1090 – 1099.

Boschelli, D.H.; Connor, D.T.; Bornemeicr, D.A.; Dyer, R.D.; Kennedy, J.A.; Kuipers, P.I.; Okonkwo, G.C.; Shrier, D.J.; Wright, C.D. (1993): J. Med. Chem. 36, 1802— 1810.

Witkowski, J.T.; Robins, R.K.; Khare, G.P.; Sidwcll, R.W. (1973): J. Med. Chem. 16, 935-937.

Shams El-Din, S.A.; Hazzaa, A.A.B. (1974): Pharmazie 29, 761-768.

Kaneko, S.; Okumura, K.; Numaguchi, Y.; Matsui, H.; Murase, K.; Mokumo, S.; Morishima, I.; Hira, K.; Toki, Y.; Ito, T.; Hayakawa, T. (2000): Life Sci**.** 67, 101-112.

Young, R.W.; Wood, K.H. (1955): *J. Am. Chem. Soc.* 77, 400.

Kassem, E.; El-masry, A.H. (1995): *Proceedings of the First International Scientific Conference (Science and Development)* Cairo, 20-23 March, 119.

El-masry, A.H.; Fahmy, H.H.; Ali Abdelwahed, S.H. (2000): *Molecules* 5, 1429-1438.

Koparir, M.; Cetin, A.; Cansiz, A.. (2005): *Molecules* 10, 475-480.

Misra, U.; Hitkari, A.; Saxena, A.; Gurtu, S.; Shanker, K. (1996): *Eur J Med Chem.* 31, 629-634.

Takamatsu, T.W.; Hodges, I.; Rajbhandari, W.H.; Gerwick, M.T.; Hamann D.G. (2003): *J. Nat. Prod*. 66, 605-608.

Jerchel, D.; Kracht, M.; Krucker, K. (1954): UntersuchungenQber benzimidazole. Jus. Lie. *Ann. Chem.* 590, 232-241.

ARABIC SUMMARY

تشييد بعض مشتقات البنزميدازول والاندول المحتوية على حلقة ترايازول ودراسة فاعليتها كمضادات للاكسدة ،

للسادة الدكاترة

محمد مختار آمن سعيد[1] - نجاة غريب عبادى[1] - بيير حنا[2] - عادل عباس الجندي[3]

مـــن

[1] قسم الكيمياء العضوية- كلية الصيدلة- جامعة قناة السويس - الاسماعيلية- مصر

[2] قسم الصيدلانيات- كلية الصيدلة- جامعة قناة السويس - الاسماعيلية- مصر

[3] قسم الكيمياء العضوية - كلية الصيدلة- جامعة مصرالدولية- القاهرة- مصر

تفاعل اوكساديازول (11) و (4 a-c)مع هيدرازين هيدرات ادى الى ترايازول(12) و(5a-c) على التوالى .تم تحويل (12)و(5a-c) الى (14و13) و (6 a-c و 7a-b) وذلك بالتفاعل مع نفثالين (3) واورثوفورمات على التوالى . تم تحويل بنزميدازول (8) الى ترايازول (9) بالتفاعل مع هيدرازين هيدرات وذلك لاختبارهم كمضادات للاكسدة فوجد ان المشتقات الجديدة لها تاثيرات متباينة ضد الاكسدة وقد امكن اثبات التركيب البنائى للمركبات الجديدة بطرق مختلفة منها تحليل العناصر الدقيقة ومطياف الكتلة والرنين النووى المغناطيسى وكذلك الاشعة تحت الحمراء.