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ENAMINONES AS BUILDING BLOCKS IN HETEROCYCLIC PREPARATIONS: SYNTHESIS OF NOVEL PYRAZOLES, PYRAZOLO-[3,4-*d*]PYRIDAZINES, PYRAZOLO[1,5-*a*]PYRIMIDINES, PYRIDO[2,3-*d*]PYRIMIDINES LINKED TO IMIDAZO[2,1-*b*]THIAZOLE SYSTEM

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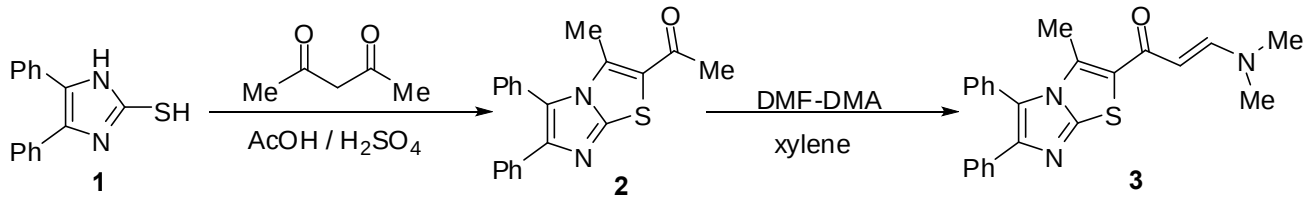
Abstract – The unreported 2-[*E*-3-(*N*,*N*-dimethylamino)acryloyl]-3-methyl-5,6-diphenylimidazo[2,1-*b*]thiazole **3** was prepared *via* the reaction of 2-acetyl-3-methyl-5,6-diphenylimidazo[2,1-*b*]thiazole **2** with dimethylformamide dimethyl acetal (DMF-DMA). Enaminone **3** underwent regioselective 1,3-dipolar cycloaddition with nitrilimines **5a-f**, to afford the corresponding pyrazoles **7a-f**. The reaction of **7a**,**d**,**g** with hydrazine hydrate, afforded the pyrazolo[3,4-*d*]pyridazines **8a-c**, respectively. Enaminone **3** also reacted with a hydrazines, hydroxylamine hydrochloride, 5-aminopyrazole **11**, 6-aminothiouracil **15** and hippuric acid **22**. The structures of the newly synthesized compounds were confirmed by spectral data and elemental analyses.

Enaminones are poly-dentate reagents that have been utilized extensively in this decade as building blocks in organic synthesis.[1-9] Furthermore, many enaminones were found to exhibit several biological activities as antitumor, antibacterial and anticonvulsant agents.[10,11]

On the other hand, imidazoles possess important biological, pharmacological and therapeutic activities,[12,13] where midazoles are present in compounds that have antiasthmatic,[16] anti-inflammatory,[17] antiulcerative,[18] antithrombotic,[19] fungicidal[20] and herbicidal activities.[21] Furthermore, some imidazo[2,1-*b*]thiazoles were active against various cancer cell lines.[22] Much interest has also been focused on the chemistry and anticonvulsant, analgesic,[23] antibacterial[24] and antisecretory[25] activities displayed by

compounds incorporating this heterocyclic system. Moreover, this system is similar in to *Levamisole*, a well-known immunomodulator.[26] In continuation of our recent work aiming at the synthesis of a variety of heterocyclic ring systems with remarkable biological importance,[27-39] in the present paper we planed to incorporate the imidazo[2,1-*b*]thiazole moiety with the title derivatives to combine the benefits of their effects to give a compact structure with expected biological activity.

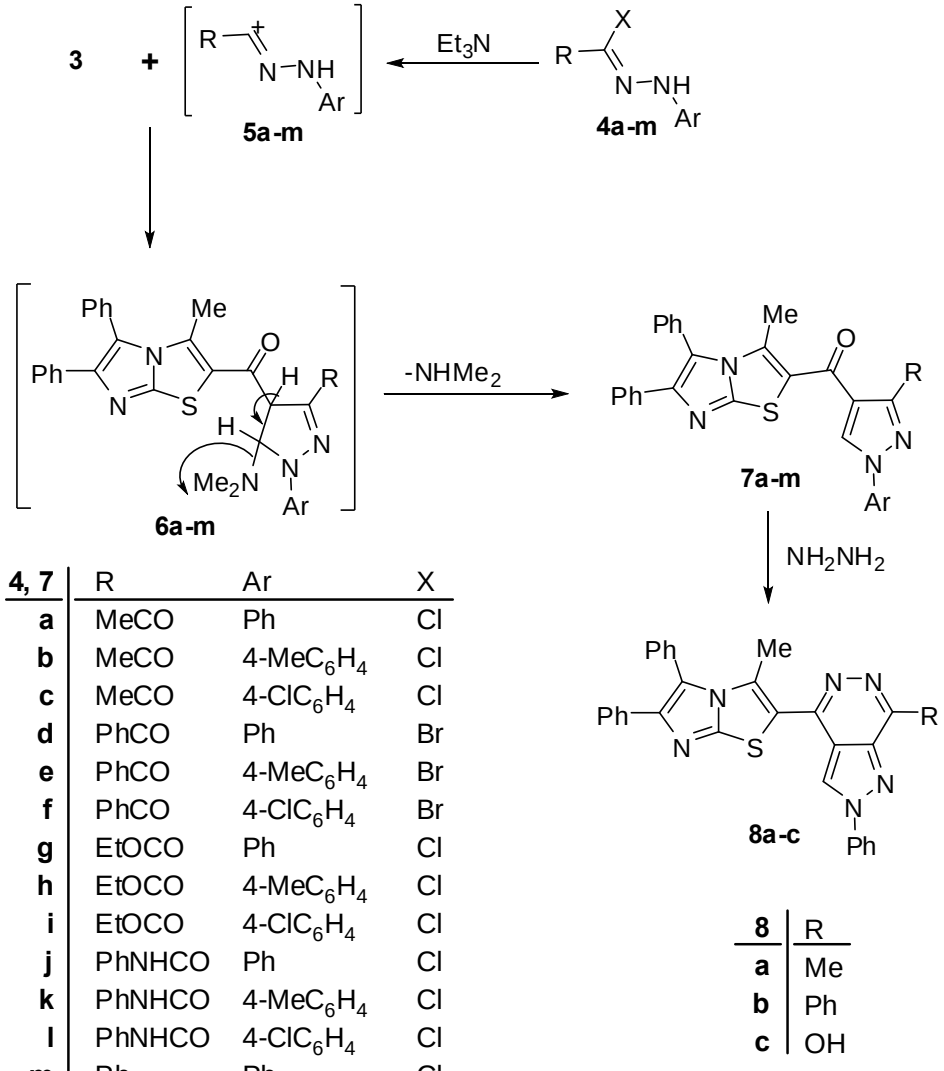
In the course of our investigation, we have found that the 2-[*E*-3-(*N*,*N*-dimethylamino)acryloyl]-3-methyl-5,6-diphenylimidazo[2,1-*b*]thiazole (**3**) is an excellent building block for the synthesis of a variety of heterocyclic ring systems. The enaminone derivative **3** was obtained from the reaction of 2-acetyl-3-methyl-5,6-diphenylimidazo[2,1-*b*]thiazole (**2**)[40] with dimethylformamide dimethyl acetal (DMF-DMA) (Scheme 1). The structure of compound **3** was confirmed by its elemental analysis and spectral data. For example, the ^{1}H NMR spectrum revealed two doublet signals at δ 5.35, 7.76 ppm with coupling constant, J = 12.5 Hz assignable to olefinic protons (CH=CH) in *E*-configuration[41-43] besides two singlet signals of the dimethylamino group at δ 2.89 and 3.16 ppm.



Scheme 1

Treatment of the enaminone **3** with nitrilimines **5a-m**, [liberated in situ from the corresponding hydrazonyl halides **4a-m**, respectively, with triethylamine in refluxing toluene], it afforded the 3,4-disubstituted-1*H*-pyrazoles **7a-m**, respectively (Schemes 2). The latter reaction products were assumed to be formed *via* initial 1,3-dipolar cycloaddition of the nitrilimines **5a-m** to the activated double bond in compound **3** to afford the non-isolable cycloadducts **6a-m** which undergoes loss of dimethylamine yielding the final pyrazole derivatives **7a-m**.[44-46]

The ^{1}H NMR spectra of the isolated products **7a-m** revealed, in each case a singlet signal in the region of 8.40-8.72 ppm which indicates the presence of the pyrazole H-5 rather than H-4. This conclusion was further confirmed chemically by the reaction compounds **7a**,**d**,**g** with hydrazine hydrate, to afford pyrazolo[3,4-*d*]pyridazines **8a-c**, respectively (Scheme 2).



4, 7	R	Ar	X
a	MeCO	Ph	Cl
b	MeCO	4-MeC_6H_4	Cl
c	MeCO	4-ClC_6H_4	Cl
d	PhCO	Ph	Br
e	PhCO	4-MeC_6H_4	Br
f	PhCO	4-ClC_6H_4	Br
g	EtOCO	Ph	Cl
h	EtOCO	4-MeC_6H_4	Cl
i	EtOCO	4-ClC_6H_4	Cl
j	PhNHCO	Ph	Cl
k	PhNHCO	4-MeC_6H_4	Cl
l	PhNHCO	4-ClC_6H_4	Cl
m	Ph	Ph	Cl

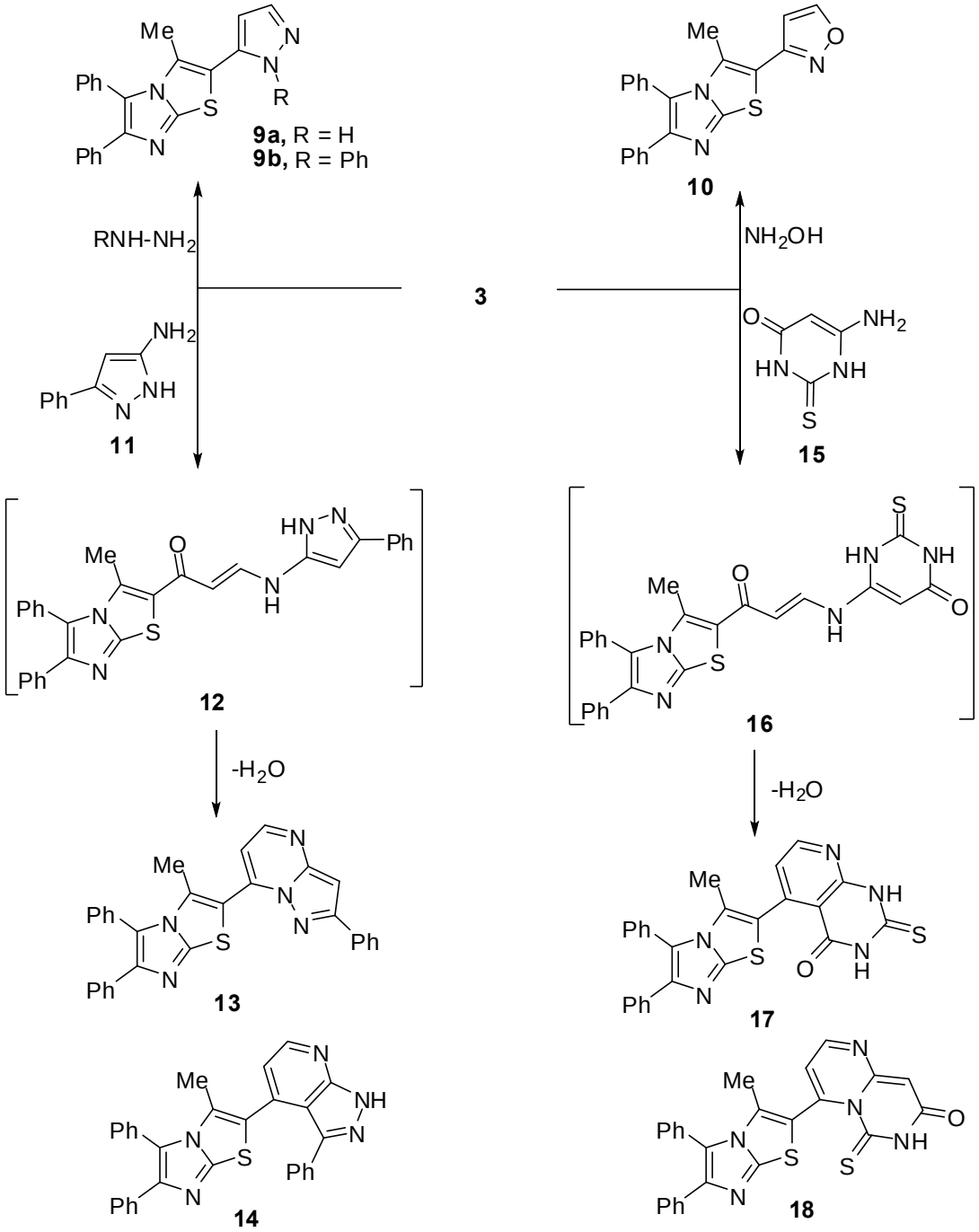
8	R
a	Me
b	Ph
c	OH

Scheme 2

Treatment of enaminone **3** with *N*-nucleophile such as hydrazine hydrate and phenylhydrazine in absolute ethanol under reflux afforded pyrazoles **9a** and **9b**, respectively. The structures of the products were substantiated by the ^{1}H NMR spectra which displayed new pair of doublets at δ 6.53 and 7.85 ppm with *J* = 7.5 Hz corresponding to pyrazole protons at positions 4 and 5, respectively. The products were formed *via* initial addition of the amino group in hydrazine to the enaminone double bond, followed by elimination of dimethylamine and water molecules to give the final isolable products **9a,b** as previously mentioned[47] (Scheme 3).

Similarly, enaminone **3** reacted with hydroxylamine hydrochloride in refluxing absolute ethanol in the presence of anhydrous potassium carbonate to yield isoxazole **10**. It is thus assumed that, the product **10** was formed *via* initial condensation of amino group of hydroxylamine with carbonyl group of enaminone **3** followed by elimination of dimethylamine (Scheme 3). Structure **10** was assigned for the reaction

products on the basis of the ^{1}H NMR spectral data in which a resonance for H-4 and H-5 of isoxazole appeared typically at δ 6.68 and 8.45 ppm, respectively.[48]



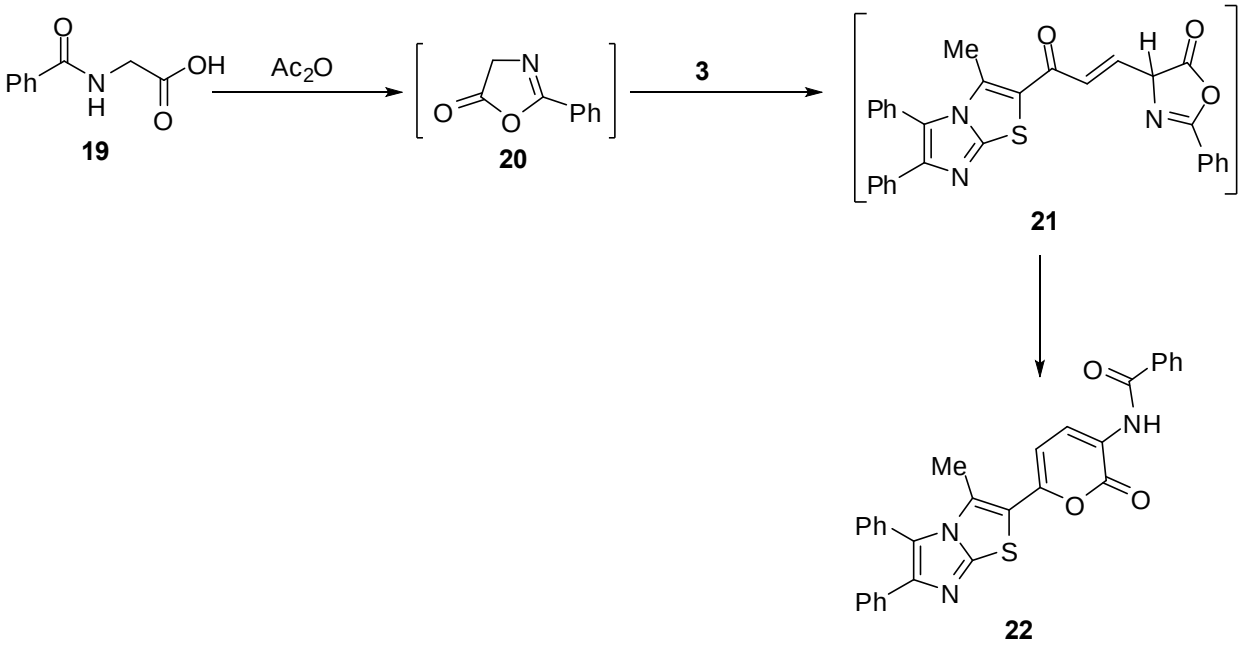
Scheme 3

The behavior of compound **3** towards aminopyrazole derivative **11** as potential precursors for the interesting biologically active pyrazolo[1,5-*a*]pyrimidines[49] was also investigated. Thus, when the enaminone **3** was treated with 5- amino-3-phenyl-1*H*-pyrazole **11** in refluxing acetic acid, it afforded 3-

methyl-5,6-diphenyl-2-(2-phenylpyrazolo[1,5-*a*]pyrimidin-6-yl)imidazo[2,1-*b*]thiazole (**13**) (Scheme 3). The structure of the latter compound was established on the basis of its elemental analysis and spectral data which exclude the other possible structure **14** (see Experimental).

We have also investigated the reaction of enaminone **3** with 6-amino-2-thioxo-(1*H*)-pyrimidin-4-one (**14**) which produced 2,3-dihydro-5-(1-naphthalenyl)-2-thioxopyrido[2,3-*d*]pyrimidin-4(1*H*)-one (**17**) or the isomeric structure **18** (Scheme 3). The ^{1}H NMR spectrum of the latter reaction product revealed a doublet signal at δ 8.30 ppm assigned to a pyridine H-2 proton and not a pyridine H-4 proton.[49] which is consistent with isomeric structure **17**. In addition, according to literature reports the reaction of heterocyclic amines to the double bond of the enaminone occurs with concurrent elimination of dimethylamine rather than condensation of a water molecule.[50,51] On the basis of these findings, structure of **18** was discarded and the product isolated from the studied reaction was assigned structure **17**.

Next, treatment of the enaminone **3** with hippuric acid **19** in refluxing acetic anhydride led to the formation of a product that was assigned the *N*-(6-(3-methyl-5,6-diphenylimidazo[2,1-*b*]thiazol-2-yl)-2-oxo-2*H*-pyran-3-yl)benzamide (**22**).[52] This structure of the latter compound was confirmed on the basis of its elemental analysis and spectral data (see Experimental). Compound **22** is assumed to be formed *via* the reaction of the intermediate oxazolone **20** which is formed in *situ* with the enaminone **3**, yielding the non-isolable intermediate **21**, that further rearranges into the pyranone **22** (Scheme 4).



Scheme 4

EXPERIMENTAL

All melting points were measured on a Gallenkamp melting point apparatus. The infrared spectra were recorded in potassium bromide disks on a Pye Unicam SP 3300 and Shimadzu FT IR 8101 PC infrared spectrophotometers. The NMR spectra were recorded on a Varian Mercury VX-300 NMR spectrometer. ^{1}H NMR and ^{13}C NMR (300 MHz) were run in deuterated dimethylsulphoxide (DMSO-d_6). Chemical shifts were related to that of the solvent. Mass spectra were recorded on a Shimadzu GCMS-QP 1000 EX mass spectrometer at 70 e.V. Elemental analyses were carried out at the Microanalytical Center of Cairo University, Giza, Egypt. 2-Acetyl-3-methyl-5,6-diphenylimidazo[2,1-*b*]thiazole (**2**),[40] hippuric acid (**19**)[53] and hydrazonoyl halides **4a-m**[54-57] were prepared following the procedures reported in the literature.

2-[*E*-3-(*N*,*N*-dimethylamino)acryloyl]-3-methyl-5,6-diphenylimidazo[2,1-*b*]thiazole (3). A mixture of the 2-acetyl-3-methyl-5,6-diphenylimidazo[2,1-*b*]thiazole (**2**) (3.32 g, 10 mmol) and dimethylformamide dimethyl acetal (DMF-DMA) (1.19 g, 10 mmol) in dry xylene (30 mL) was refluxed for 3 h, then allowed to cool. The yellow precipitate was filtered off, washed with petroleum ether (60/80 ^{o}C), dried and crystallized from EtOH to afford compound **3**. Yield 86%; mp 224 ^{o}C; IR (KBr) ν cm^{-1}: 1654 (C=O); ^{1}H NMR (DMSO-d_6) δ: 2.17 (s, 3H, CH_3), 2.89 (s, 3H, CH_3), 3.16 (s, 3H, CH_3), 5.35 (d, 1H, CH, J = 12.5 Hz), 7.22-7.64 (m, 10H, ArH's), 7.76 (d, 1H, CH, J = 12.5 Hz); MS *m/z* (%): 389 (M^++2, 4), 388 (M^++1, 6), 387 (M^+, 20), 237 (7), 136 (31), 98 (100), 55 (63). Anal. Calcd for $C_{23}H_{21}N_3OS$ (387.14): C, 71.29; H, 5.46; N, 10.84. Found: C, 71.08; H, 5.24; N, 10.46%.

Synthesis of 2-[(1,3-disubstituted-1*H*-4-pyrazolyl)carbonyl]-3-methyl-5,6-diphenylimidazo[2,1-*b*]thiazole derivatives (7a-m).

To a stirred solution of the appropriate enaminone derivative **3** (10 mmol) and the appropriate hydrazonoyl halides **4a-m** (10 mmol) in toluene (20 mL), an equivalent amount of triethylamine (0.5 mL) was added. The reaction mixture was heated under reflux for 6 h. The precipitated triethylamine hydrochloride was filtered off, and the filtrate was evaporated under reduced pressure. The residue was triturated with MeOH. The solid product, so formed in each case, was collected by filtration, washed with water, dried, and crystallized from EtOH to afford the corresponding pyrazole derivatives **7a-m**.

2-[(3-Acetyl-1-phenyl-1*H*-4-pyrazolyl)carbonyl]-3-methyl-5,6-diphenylimidazo[2,1-*b*]thiazole (7a): Yield 78%; mp 236 ^{o}C; IR (KBr) ν cm^{-1}: 1712, 1646 (2C=O); ^{1}H NMR (DMSO-d_6) δ: 2.18 (s, 3H, CH_3), 2.54 (s, 3H, $COCH_3$), 7.22-7.64 (m, 15H, ArH's), 8.42 (s,1H, pyrazole-H5); ^{13}C NMR (DMSO-d_6): δ 12.61 (CH_3), 28.42 (CH_3), 114.45, 120.27, 120.59, 121.25, 121.85, 122.34, 123.34, 123.85, 124.33, 125.75, 127.16, 127.31, 128.63, 128.61, 129.10, 129.31, 130.73, 133.61, 138.73, 142.61 (Ar-C), 189.82 (C=O), 192.51 (C=O); MS *m/z* (%): 503 (M^++1, 12), 502 (M^+, 32), 228 (27), 136 (31), 101 (58), 55 (100). Anal. Calcd for $C_{30}H_{22}N4O_2S$ (502.15): C, 71.69; H, 4.41; N, 11.15. Found: C, 71.51; H, 4.23; N,

11.33%.

2-[(3-Acetyl-1-(4-tolyl)-1*H*-4-pyrazolyl)carbonyl]-3-methyl-5,6-diphenylimidazo[2,1-*b*]thiazole (7b): Yield 82%; mp 136 °C; IR (KBr) *v* cm^{-1}: 1708, 1646 (2C=O); ^{1}H NMR (DMSO-d_6) δ: 2.19 (s, 3H, CH_3), 2.34 (s, 3H, $ArCH_3$), 2.54 (s, 3H, $COCH_3$), 7.20-7.62 (m, 14H, ArH's), 8.40 (s, 1H, pyrazole-H5); MS *m/z* (%): 516 (M^+, 58), 227 (75), 104 (58), 55 (100). Anal. Calcd for $C_{31}H_{24}N_4O_2S$ (516.16): C, 72.07; H, 4.68; N, 10.85 . Found: C, 71.90; H, 4.51; N, 10.72%.

2-[(3-Acetyl-1-(4-chlorophenyl)-1*H*-4-pyrazolyl)carbonyl]-3-methyl-5,6-diphenylimidazo[2,1-*b*]-thiazole (7c): Yield 81%; mp 178 °C; IR (KBr) *v* cm^{-1}: 1708, 1648 (2C=O); ^{1}H NMR (DMSO-d_6) δ: 2.18 (s, 3H, CH_3), 2.53 (s, 3H, $COCH_3$), 7.21-7.66 (m, 14H, ArH's), 8.43 (s, 1H, pyrazole-H5); MS *m/z* (%): 537 (M^++1, 13), 536 (M^+, 45), 227 (34), 104 (39), 98 (100). Anal. Calcd for $C_{30}H_{21}ClN_4O_2S$ (536.11): C, 67.09; H, 3.94; N, 10.43. Found: C, 67.01; H, 3.90; N, 10.26%.

2-[(3-Benzoyl-1-phenyl-1*H*-4-pyrazolyl)carbonyl]-3-methyl-5,6-diphenylimidazo[2,1-*b*]thiazole (7d): Yield 82%; mp 184 °C. IR (KBr) *v* cm^{-1}: 1698, 1650 (2C=O). ^{1}H NMR (DMSO-d_6) δ: 2.20 (s, 3H, CH_3), 7.23-7.57 (m, 20H, ArH's), 8.46 (s, 1H, pyrazole-H5); ^{13}C NMR (DMSO-d_6): *δ* 12.24 (CH_3), 114.65, 120.68, 120.91, 121.13, 121.67, 122.13, 123.14, 123.67, 123.87, 124.02, 124.35, 124.65, 125.24, 125.78, 127.11, 127.38, 128.77, 128.82, 129.17, 130.11, 130.70, 133.21, 139.87, 140.67 (Ar-C), 178.99 (C=O), 188.65 (C=O); MS *m/z* (%): 564 (M^+, 13), 304 (10), 136 (37), 98 (100), 77 (53). Anal. Calcd for $C_{35}H_{24}N_4O_2S$ (564.16): C, 74.45; H, 4.28; N, 9.92. Found: C, 74.30; H, 4.10; N, 9.70%.

2-[(3-Benzoyl-1-(4-tolyl)-1*H*-4-pyrazolyl)carbonyl]-3-methyl-5,6-diphenylimidazo[2,1-*b*]thiazole (7e): Yield 82%; mp 178 °C. IR (KBr) *v* cm^{-1}: 1696, 1651 (2C=O); ^{1}H NMR (DMSO-d_6) δ: 2.21 (s, 3H, CH_3), 2.32 (s, 3H, $ArCH_3$), 7.21-7.58 (m, 19H, ArH's), 8.44 (s, 1H, pyrazole-H5); MS *m/z* (%): 578 (M^+, 5), 386 (53), 194 (10), 98 (65), 77 (100). Anal. Calcd for $C_{36}H_{26}N_4O_2S$ (578.18): C, 74.72; H, 4.53; N, 9.68. Found: C, 74.55; H, 4.31; N, 9.45%.

2-[(3-Benzoyl-1-(4-chlorophenyl)-1*H*-4-pyrazolyl)carbonyl]-3-methyl-5,6-diphenylimidazo[2,1-*b*]-thiazole (7f): Yield 82%; mp 198 °C; IR (KBr) *v* cm^{-1}: 1698, 1654 (2C=O); ^{1}H NMR (DMSO-d_6) δ: 2.20 (s, 3H, CH_3), 7.21-7.57 (m, 19H, ArH's), 8.45 (s, 1H, pyrazole-H5). MS *m/z* (%): 598 (M^+, 5), 386 (53), 136 (39), 98 (100), 77 (54); Anal. Calcd for $C_{35}H_{23}ClN_4O_2S$ (598.12): C, 70.17; H, 3.87; N, 9.35%. Found: C, 70.01; H, 3.80; N, 9.30%.

2-[(3-Ethoxycarbonyl-1-phenyl-1*H*-4-pyrazolyl)carbonyl]-3-methyl-5,6-diphenylimidazo[2,1-*b*]-thiazole (7g): Yield 77%; mp 166 °C; IR (KBr) *v* cm^{-1}: 1714, 1648 (2C=O); ^{1}H NMR ($CDCl_3$) δ: 1.20 (t, 3H, CH_3, *J* = 7.1 Hz), 2.20 (s, 3H, CH_3), 4.32 (q, 2H, CH_2, *J* = 7.1 Hz), 7.20-7.64 (m, 15H, ArH's), 8.61 (s, 1H, pyrazole-H5); ^{13}C NMR (DMSO-d_6): *δ* 12.11 (CH_3), 14.82 (CH_3), 63.84 (CH_2), 116.34, 119.83, 120.48, 121.35, 121.89, 122.21, 123.24, 123.65, 124.16, 125.43, 127.24, 127.56, 127.81, 128.61, 129.17,

129.04, 130.34, 134.41, 138.95, 143.58 (Ar-C), 169.53 (C=O), 186.32 (C=O); MS *m/z* (%): 532 (M^+, 47), 366 (68), 324 (25), 191(49), 148 (100), 77 (45). Anal. Calcd for $C_{31}H_{24}N_4O_3S$ (532.16): C, 69.91; H, 4.54; N, 10.52. Found: C, 69.71; H, 4.53; N, 10.39%.

2-[(3-Ethoxycarbonyl-1-(4-tolyl)-1*H*-4-pyrazolyl)carbonyl]-3-methyl-5,6-diphenylimidazo[2,1-*b*]-thiazole (7h): Yield 77%; mp 172 °C; IR (KBr) *v* cm^{-1}: 1715, 1648 (2C=O); ^1H NMR ($CDCl_3$) δ: 1.17 (t, 3H, CH_3, *J* = 7.1 Hz), 2.20 (s, 3H, CH_3), 2.33 (s, 3H, $ArCH_3$), 4.30 (q, 2H, CH_2, *J* = 7.1 Hz), 7.20-7.64 (m, 14H, ArH's), 8.62 (s, 1H, pyrazole-H5); MS *m/z* (%): 546 (M^+, 47), 366 (54), 323 (29), 191(34), 148 (51), 77 (100). MS *m/z* (%): 546 (M^+, 12), 456 (71), 428 (23), 272 (20), 77 (100). Anal. Calcd for $C_{32}H_{26}N_4O_3S$ (546.17): C, 70.31; H, 4.79; N, 10.25. Found: C, 70.19; H, 4.70; N, 10.15%.

2-[(3-Ethoxycarbonyl-1-(4-chlorophenyl)-1*H*-4-pyrazolyl)carbonyl]-3-methyl-5,6-diphenylimidazo-[2,1-*b*]thiazole (7i): Yield 70%; mp 178 °C. IR (KBr) *v* cm^{-1}: 1718, 1649 (2C=O); ^1H NMR (DMSO-d_6) δ: 1.17 (t, 3H, CH_3, *J* = 7.1 Hz), 2.21 (s, 3H, CH_3), 4.25 (q, 2H, CH_2, *J* = 7.1 Hz), 7.22-7.68 (m, 14H, ArH's), 8.62 (s, 1H, pyrazole-H5); MS *m/z* (%): 567 (M^++1,7), 566 (M^+, 23), 249 (21), 180 (19), 184 (100), 77 (43). Anal. Calcd for $C_{31}H_{23}ClN_4O_3S$ (566.12): C, 65.66; H, 4.09; N, 9.88%. Found: C, 65.55; H, 3.98; N, 9.60%.

2-[(3-phenylcarbamoyl-1-phenyl-1*H*-4-pyrazolyl)carbonyl]-3-methyl-5,6-diphenylimidazo[2,1-*b*]-thiazole (7j): Yield 77%; mp 222 °C; IR (KBr) *v* cm^{-1}: 3246 (NH), 1693, 1652 (2C=O); ^1H NMR (DMSO-d_6) δ: 2.16 (s, 3H, CH_3), 7.16-7.72 (m, 20H, ArH's), 8.52 (s, 1H, pyrazole-H5), 10.84 (br., s, 1H, NH, D_2O-exchangeable); MS *m/z* (%): 580 (M^++1, 1), 579 (M^+, 1), 384 (97), 305 (12), 178 (100), 77 (13). Anal. Calcd for $C_{35}H_{25}N_5O_2S$ (579.17): C, 72.52; H, 4.35; N, 12.08. Found: C, 72.48; H, 4.21; N, 12.00%.

2-[(3-phenylcarbamoyl-1-(4-tolyl)-1*H*-4-pyrazolyl)carbonyl]-3-methyl-5,6-diphenylimidazo[2,1-*b*]-thiazole (7k): Yield 72%; mp 228 °C; IR (KBr) *v* cm^{-1}: 3252 (NH), 1688, 1649 (2 C=O); ^1H NMR (DMSO-d_6) δ: 2.16 (s, 3H, CH_3), 2.38 (s, 3H, $ArCH_3$), 7.15-7.93 (m, 19H, ArH's), 8.72 (s, 1H, pyrazole-H5), 11.50 (br., s, 1H, NH, D_2O-exchangeable); MS *m/z* (%): 593 (M^+, 5), 456 (100), 428 (17), 244 (43), 77 (87). Anal. Calcd for $C_{36}H_{27}N_5O_2S$ (593.19): C, 72.83; H, 4.58; N, 11.80%. Found: C, 72.67; H, 4.55; N, 11.36%.

2-[(3-phenylcarbamoyl-1-(4-chlorophenyl)-1*H*-4-pyrazolyl)carbonyl]-3-methyl-5,6-diphenylimidazo-[2,1-*b*]thiazole (7l): Yield 83%; mp 236 °C; IR (KBr) *v* cm^{-1}: 3256 (NH), 1689, 1651 (2C=O); ^1H NMR (DMSO-d_6) δ: 2.18 (s, 3H, CH_3), 7.25-7.90 (m, 19H, ArH's), 8.72 (s, 1H, pyrazole-H5), 11.21 (br., s, 1H, NH, D_2O-exchangeable); MS *m/z* (%): 613 (M^+, 8), 568 (M^+, 19), 476 (88), 272 (22) 180 (5), 141 (25), 77 (100). Anal. Calcd for $C_{35}H_{24}ClN_5O_2S$ (613.13): C, 68.45; H, 3.94; N, 11.40. Found: C, 68.39; H, 3.87; N, 11.36%.

2-[(1,3-Diphenyl-1*H*-4-pyrazolyl)carbonyl]-3-methyl-5,6-diphenylimidazo[2,1-*b*]thiazole (7m): Yield 69%; mp 224 °C; IR (KBr) *v* cm^{-1}: 1678 (C=O); ^{1}H NMR (DMSO-d_6) δ: 2.18 (s, 3H, CH_3), 7.18-7.73 (m, 20H, ArH's), 8.68 (s, 1H, pyrazole-H5); MS *m/z* (%): 538 (M^++2, 86), 537 (M^++1, 71), 536 (M^+, 71), 498 (57), 398 (71), 76 (100). Anal. Calcd for $C_{34}H_{24}N_4OS$ (536.17): C, 76.10; H, 4.51; N, 10.44. Found: C, 76.12; H, 4.31; N, 10.23%.

Reaction of pyrazoles 7a,d,g with hydrazine hydrate

Hydrazine hydrate (80%, 2 mL) was added to a solution of the appropriate compound **7a,d,g** (5 mmol) in EtOH (10 mL). The reaction mixture was heated under reflux for 1 h, concentrated in vacuum, and diluted with water. The precipitate obtained was filtered off, washed with ice-cold water, dried and crystallized from EtOH. The synthesized pyrazolo[3,4-*d*]pyridazines **10a-c** together with their physical and spectral data are listed below.

3-Methyl-2-(7-methyl-2-phenyl-2*H*-pyrazolo[3,4-*d*]pyridazin-4-yl)-5,6-diphenylimidazo[2,1-*b*]-thiazole (8a): Yield 72%; mp 268 °C; ^{1}H NMR (DMSO-d_6) δ: 2.19 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 7.20-7.37 (m, 15H, ArH's), 8.64 (s, 1H, pyrazole-H5); MS *m/z* (%): 498 (M^+, 100), 284 (57), 77 (74). Anal. Calcd for $C_{30}H_{22}N_6S$ (498.16): C, 72.27; H, 4.45; N, 16.86. Found: C, 72.20; H, 4.43; N, 16.79%.

2-(2,7-Diphenyl-2*H*-pyrazolo[3,4-*d*]pyridazin-4-yl)-3-methyl-5,6-diphenylimidazo[2,1-*b*]thiazole (8b): Yield 70%; mp 242 °C; ^{1}HNMR (DMSO-d_6) δ: 2.19 (s, 3H, CH_3), 7.20-7.37 (m, 20H, ArH's), 8.60 (s, 1H, pyrazole-H5); ^{13}C NMR (DMSO-d_6): δ 12.16 (CH_3), 113.46, 118.87, 120.34, 120.87, 121.67, 122.65, 123.01, 123.32, 123.49, 124.14, 124.43, 124.75, 125.24, 125.88, 127.38, 127.76, 128.77, 128.52, 129.87, 130.23, 131.56, 134.58, 139.24, 143.16, 148.36, 152.24 (Ar-C); MS *m/z* (%): 560 (M^+, 100), 398 (37), 295 (14), 180 (11), 77 (95). Anal. Calcd for $C_{35}H_{24}N_6S$ (560.18): C, 74.98; H, 4.31; N, 14.99. Found: C, 74.85; H, 4.27; N, 14.85%.

4-(3-Methyl-5,6-diphenylimidazo[2,1-*b*]thiazol-2-yl)-2-phenyl-2*H*-pyrazolo[3,4-*d*]pyridazin-7(6*H*)-one (8c): Yield 76%; mp 221 °C; IR (KBr) *v* cm^{-1}: 3350 (OH); ^{1}H NMR (DMSO-d_6) δ: 2.19 (s, 3H, CH_3), 2.98 (br., s, 1H, OH, D_2O-exchangeable), 7.17-7.39 (m, 15H, ArH's), 8.64 (s, 1H, pyrazole H-5), 11.00 (br., s, 1H, NH, D_2O-exchangeable); MS *m/z* (%): 500 (M^+, 100), 398 (37), 295 (14), 180 (14), 77 (84). Anal. Calcd for $C_{29}H_{20}N_6OS$ (500.14): C, 69.58; H, 4.03; N, 16.79 . Found: C, 69.55; H, 3.97; N, 16.65%.

Reactions of enaminone 3 with hydrazines

To a solution of the enaminone **3** (0.387 g, 1 mmol) in EtOH (10 mL) was added hydrazine hydrate (1 mL) or phenylhydrazine (1 mL) and the mixture was heated under reflux for 2 h. The reaction mixture was acidified by HCl / ice mixture and the formed product was filtered and crystallized from EtOH to give the respective pyrazoles **9a** and **9b**.

3-Methyl-5,6-diphenyl-2-(1*H*-pyrazol-3-yl)imidazo[2,1-*b*]thiazole (9a): Yield 90%, mp 250 °C; IR (KBr) υ: 3226 (NH) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ: 2.03 (s, 3H, CH_3), 6.53 (d, 1H, *J* = 7.5 Hz, pyrazole-H4), 7.14–7.61 (m, 10H, Ar-H), 7.85 (d, 1H, *J* = 7.5 Hz, pyrazole-H5), 13.12 (D_2O-exchangeable) (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6): *δ* 12.32 (CH_3), 114.35, 120.57, 121.03, 122.34, 123.75, 124.86, 126.75, 127.45, 127.76, 128.81, 129.16, 129.38, 130.54, 135.31, 138.73, 145.33 (Ar-C); MS *m/z* (%): 357 (M^++1, 27), 356 (M^+, 100), 227 (14), 152 (52), 103 (29). Anal. Calcd for $C_{21}H_{16}N_4S$ (356.11): C, 70.76; H, 4.52; N, 15.72. Found: C, 70.67; H, 4.41; N, 15.62%.

3-Methyl-5,6-diphenyl-2-(1-phenyl-1*H*-pyrazol-3-yl)imidazo[2,1-*b*]thiazole (9b): Yield 86%, mp 264 °C; ^{1}H NMR (DMSO-d_6) δ: 2.12 (s, 3H, CH_3), 6.51 (d, 1H, *J* = 7.5 Hz, pyrazole H-4), 7.14–7.61 (m, 15H, Ar-H), 7.84 (d, 1H, *J* = 7.5 Hz, pyrazole-H5) ppm; MS *m/z* (%): 432 (M^+, 100), 227 (14), 152 (36), 103 (54), 641(29). Anal. Calcd for $C_{27}H_{20}N_4S$ (432.14): C, 74.97; H, 4.66; N, 12.95. Found: C, 74.69; H, 4.45; N, 12.68%.

2-(3-Isoxazolyl)-3-methyl-5,6-diphenylimidazo[2,1-*b*]thiazole (10): Hydroxylamine hydrochloride (0.07 g, 1 mmol) was added to a mixture of enaminone (**3**) (0.387 g, 1 mmol) and anhydrous potassium carbonate (0.5 g) in absolute EtOH (20 mL). The mixture was heated under reflux for 5 h and poured onto water. The solid product was filtered and crystallized from EtOH to give compound **10** in 90% yield, mp: 212 °C; ^{1}H NMR (DMSO-d_6) δ: 2.14 (s, 3H, CH_3), 6.68 (d, 1H, *J* = 5 Hz, isoxazole- H4), 7.14-7.68 (m, 10H, Ar-H), 8.45 (d, 1H, *J* = 5 Hz, isoxazole-H5) ppm; MS *m/z* (%): 357 (M^++1, 27), 356 (M^+, 100), 227 (14), 152 (52), 103 (29). Anal. Calcd for $C_{21}H_{15}N_3OS$ (357.09): C, 70.57; H, 4.23; N, 11.76. Found: C, 70.56; H, 4.14; N, 11.39%.

Reactions of enaminone 3 with heterocyclic amines

A mixture of enaminone **3** (1.96 g, 5 mmol) and 5-amino-3-phenyl-1*H*-pyrazole (**11**) or 6-amino-2-thioxo-2,3-dihydropyrimidin-4(1*H*)-one (**15**) (5 mmol) in acetic acid (20 mL) was refluxed for 6 h. The reaction mixture was cooled and diluted with MeOH and the solid product was collected by filtration and recrystallized from dioxane to give **13** or **17**, respectively.

3-Methyl-5,6-diphenyl-2-(2-phenylpyrazolo[1,5-*a*]pyrimidin-6-yl)imidazo[2,1-*b*]thiazole (13): Yield 83%, mp 312 °C; ^{1}H NMR (DMSO-d_6) δ: 1.91 (s, 3H, CH_3), 7.16 (s, 1H, pyrazole-H4), 7.21-7.66 (m, 15H, Ar-H), 8.54 (s, 1H, pyrimidine-H4), 8.59 (s, 1H, pyrimidine-H6) ppm; ^{13}C NMR (DMSO-d_6): *δ* 12.60 (CH_3), 110.36, 116.23, 120.24, 120.56, 121.48, 121.85, 123.22, 123.68, 124.35, 124.28, 125.24, 126.46, 127.29, 127.36, 128.82, 129.67, 130.23, 134.58, 139.24, 140.23, 146.24, 150.23 (Ar-C); MS *m/z* (%): 483 (M^+, 100), 352 (6), 250 (11), 217 (33), 103 (43), 63 (21). Anal. Calcd for $C_{30}H_{21}N_5S$ (483.15): C, 59.72; H, 3.19; N, 18.99. Found: C, 59.63; H, 3.10; N, 18.76%.

5-(3-Methyl-5,6-diphenylimidazo[2,1-*b*]thiazol-2-yl)-2-thioxo-2,3-dihydropyrido[2,3-*d*]pyrimidin-4(1*H*)-one (17): Yield 86%, mp 352 °C; IR (KBr) υ: 3268, 3234 (2 NH), 1676 (CO)cm^{-1}; ^{1}H NMR (DMSO-d_6) δ: 1.91 (s, 3H, CH_3), 7.17–7.59 (m, 10H, Ar-H), 7.61 (d, 1H, *J* = 7 Hz, pyridineH-3), 8.30 (d, 1H, *J* = 7 Hz, pyridine H-2),11.92 (s, 1H, NH), 12.58 (s, 1H, NH), 13.14 (s, 1H, SH tautomer of C=S) ppm; MS *m/z* (%): 468 (M^++1, 30), 468 (M^+, 100), 352 (13), 250 (13), 217(33), 165 (37), 63 (21). Anal. Calcd for $C_{25}H_{17}N_5OS_2$ (467.09): C, 64.22; H, 3.66; N, 14.98. Found: C, 64.11; H, 3.42; N, 14.69%.

***N*-(6-(3-Methyl-5,6-diphenylimidazo[2,1-*b*]thiazol-2-yl)-2-oxo-2*H*-pyran-3-yl)benzamide (22)**: A solution of enaminone **3** (3.87 g, 10 mmol) and hippuric acid (**19**) (1.7 g, 10 mmol) in acetic anhydride (30 mL) was heated under reflux for 2 h. The reaction mixture was concentrated *in vacuo*. The solid product obtained upon cooling was filtered off and recrystallized from DMF to yield compound **22** in 85% yield, mp 242 °C; IR (KBr) υ = 3294 (NH), 1698, 1668 (2 C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ: 2.14 (s, 3H, CH_3), 6.74 (d, 1H, *J* = 7.6 Hz, pyran-H5), 6.78 (d, 1H, *J* = 7.6 Hz, pyran-H4), 7.11-7.72 (m, 15H, Ar-H), 9.78 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ 12.44 (CH_3), 114.82, 120.47, 120.78, 121.47, 122.34, 123.46, 123.68, 124.45, 124.75, 124.95, 125.84, 125.97, 127.65, 127.85, 128.73, 128.97, 129.56, 131.56, 132.31, 138.34, 142.62 (Ar-C), 159.89 (C=O), 168.78 (C=O); MS, *m/z* (%): 504 (M^++1, 13), 503 (M^+, 18), 290 (18), 105 (100), 77 (66). Anal. Calcd for $C_{30}H_{21}N_3O_3S$ (503.13): C, 71.55; H, 4.20; N, 8.34. Found: C, 71.43; H, 4.12; N, 8.12%.

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