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Chemistry

SYNTHESIS AND CHARACTERIZATION OF SOME NEW 3-CHLOROBENZOTHIOPHENECARBONYL DERIVATIVES OF BENZIMIDOZOLYLPYRAZOLE

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ABSTRACT In the present investigation, synthesis of 3-chlorobenzothiophenecarbonyl derivatives of benzimidozolylpyrazole. Nucleophilic aza substitution on isatoic anhydride with p-aminoacetophenone gave 3-(4-acetylphenyl) quinazoline-2,4-dione **(I)**. This on Claisen condensation with various aromatic aldehydes **(IIa-d)** yields the corresponding 3-{4-[3-(4-substitutedphenyl) prop-2-enoyl]phenyl}quinazoline-2,4-dione **(IIIa-d)** derivatives.

This was condensed by 3-chloro-1-benzothiophene-2-carbonyl chloride to afford {3-[1-(3-chlorobenzo[b]thiophene-2-carbonyl)-1H-indole-3-yl]-4-chlorophenyl)prop-2-enoyl]phenyl}-quinazoline-2,4-dione **(IVa-d)**. These compounds **(IVa-d)** were cyclized with phenyl hydrazine in ethanolic media to give final compound **(Va-d)**. Structures of synthesized compounds have been assigned on the basis of their analytical and spectral data.

KEYWORDS : pyrazole, Quinazolin, Chalcone, 3-chlorobenzothiophenecarbonyl chloride, condensation.

Introduction:

The pyrazole ring is a prominent structural motif found in numerous pharmaceutically active compounds. This is mainly due to the ease preparation and the important biological activity. Pyrazole framework plays an essential role in biologically active compounds and therefore represents an interesting template for combinatorial as well as medicinal chemistry[1-5]. The pyrazole nucleus is a ubiquitous feature of pharmacological interest and has been proven to be a fertile source of medicinal agents such as antibacterial[6], antifungal[7], antiviral[8], antitubercular[9], antiamoebic[10], antiandrogenic[11], etc. Some of these compounds have also exhibited anti-inflammatory[12], antidiabetic[13], anaesthetic[14], analgesic[15] and antiparasitic[16] properties. Many pyrazoles have been found to be luminescent and fluorescent[17,18] agents. In addition pyrazoles have played a crucial role in the development of theory in heterocyclic chemistry and also used extensively as useful synthon in organic synthesis[19-23].

Quinazolinone derivatives attract a widespread interest due to the diverse biological Activities[24] associated with them. They are pharmaceutically important as antituberculars4, Antibacteria[25], antiparkinsons[26], antihelmintics[27], and they also show blood platelet antiaggregating activity. Pyrazolones are associated with broad spectrum of biological activities including antifungal, antibacterial, anti-inflammatory properties[28-30].

In view of above mentioned facts and in connection with 3-chloro-1-benzothiophene-2-carbonyl chloride the derivatives of heterocycles, it appeared expedient to synthesize {3-[1-(3-substituted benzo[b]thiophene-2-carbonyl)-1*H*-indole-3-yl]-4-chlorophenyl)-4,5-dihydro-1H-pyrazol-3-yl]phenyl}-quinazoline-2,4-dione **(Va-d)** via a series of reactions.

EXPERIMENTAL SECTION:

General Procedures: Melting points were taken in open capillary tubes and are therefore uncorrected. Purity of the compounds was checked on silica gel G TLC plates of 2 mm thickness using n-hexane and ethyl acetate as solvent system. The visualization of spot was carried out in an iodine chamber. The IR spectra of the compounds were recorded in the 4000-450 cm-1 ranges using KBr discs on FTIR IR RX1 Perkin Elmer spectrophotometers and 1H NMR were recorded on a Bruker DRX-300 MHz spectrometer (CDCl3) using TMS as an internal standard. The ESI-MS were recorded on a MICROMASS QUATTRO II triple quadrupole mass spectrometer having a JASCOPU-980 HPLC pump connected to it. 3-chloro-1-benzothiophene-2-carbonyl chloride[31] have been prepared by reported methods.

***Synthesis of 3-(4-acetylphenyl) quinazoline-2,4-dione* (I)**

To a solution of isatoic anhydride (0.01 mole) in absolute alcohol, *p* aminoacetophenone (0.01mole) was added. The reaction mixture was heated under reflux for 4 hrs. Excess of the solvent was distilled off under reduced pressure and after cooling crystalline product was obtained. It was filtered and recrystallized from ethanol to yield needle shaped crystals.

KBr IR: 3416 (N-H str.),3086 (C-H str., Ar-H), 2935 (C-H, str. CH_3), 1718, 1693 (C=Ostr.)

^{1}HNMR ($CDCl_3$) δ:8.6 (s, 1H, NH), 6.8-7.4 (m, 8H, Ar-H), 2.6 (s, 3H, CH_3).

***Synthesis of 3-{4-[3-(4-chlorophenyl)prop-2-enoyl]phenyl}quinazoline-2,4-dione* (IIIa-d):**

To a stirred solution of (**I,** 0.01 mol) 4-chlorobenzaldehyde (**II a**0.01 mol) in ethanol (20 ml) NaOH (3 g dissolved in minimum amount of water) was added portion wise. The stirring was continued for next 1 hrs and then kept overnight. The contents of the flask were poured into water and neutralized with acetic acid. The separated solid was filtered, washed with water, dried and recrystallized from ethanol.

Similarly, compounds **IIIb-d** also synthesized by changing stirring time.

KBr IR: 3408 (N-H str.), 3075 (C-H str., Ar-H),1658 (C=O str.), 1648-1665 (CH=CH str.), 740 (C-Cl), ^{1}HNMR ($CDCl_3$) δ: 9.20 (s, 1H, NH), 7.2-7.8 (m, 12H, Ar-H),6.8 (*d*, 1H, Ar-CH=CH), 7.5 (*d*, 1H, Ar-CH=CH),

***Synthesis of 3-{4-[3-phenylprop-2-enoyl]phenyl}quinazoline-2,4-dione* (IIIb):**

KBr IR: 3420 (N-H str.), 3062 (C-H str., Ar-H),1682 (C=O str.), 1640-1662 (CH=CH str.); ^{1}HNMR ($CDCl_3$) δ: 9.05 (s, 1H, NH), 6.8-7.3 (m, 13H, Ar-H), 6.4 (*d*, 1H, Ar-CH=CH), 7.1 (*d*, 1H, Ar-CH=CH).

***Synthesis of 3-{4-[(2E)-3-(4-methoxyphenyl)prop-2-enoyl]phenyl}quinazoline-2,4-dione*(IIIc):**

KBr IR: 3427 (N-H str.), 3068 (C-H str., Ar-H), 1690 (C=O str.), 1642-1668 (CH=CH str.), ^{1}HNMR ($CDCl_3$) δ: 9.15 (s, 1H, NH), 6.9-7.5 (m, 12H, Ar-H), 6.6 (*d*, 1H, Ar-CH=CH), 7.3 (*d*, 1H, Ar-CH=CH), 3.40 (s, 3H, OCH_3).

***Synthesis of 3-(4-{(2E)-3-[4-(N,N dimethylamino)phenyl]prop-2-enoyl}phenyl) quinazoline-2,4(1H,3H)-dione* (IIId):**

KBr IR: 3432 (N-H str.), 3083 (C-H str., Ar-H),1694 (C=O str.), 1638-1662 (CH=CH str.) ^{1}HNMR ($CDCl_3$) δ : 9.25 (s, 1H, NH), 7.0-7.6 (m, 12H, Ar-H),6.9 (*d*, 1H, Ar-CH=CH), 7.7 (*d*, 1H, Ar-CH=CH), 2.97 (s, 6H, $N(CH_3)_2$).

Synthesis of {3-[1-(3-chlorobenzo[b]thiophene-2-carbonyl)-1*H*-

indole-3-yl]-4-chloro phenyl)prop-2-enoyl]phenyl}-quinazoline-2,4-dione (Iva-d):
Compound (**IIIa,** 0.01 mole) and 3-chloro-1-benzothiophene-2-carbonyl chloride (0.01 mole), were refluxed in dry acetone for 15-17 hrs. Containing K_2CO_3 (0.01 mole) as base. It was filtered and excess of solvent was removed under reduced pressure. The separated solid was filtered, washed and recrystallized from ethanol.

Similarly, compounds **IVb-d** also synthesized by changing stirring time.

KBr IR: 3065 (C-H str., Ar-H),1648 (C=O str.), 745 (C-Cl), ^{1}HNMR ($CDCl_3$) δ: 6.8-7.6 (m, 16H, Ar-H),6.4 (*d*, 1H, Ar-CH=CH), 7.2 (*d*, 1H, Ar-CH=CH).

Synthesis of {3-[1-(3-chlorobenzo[b]thiophene-2-carbonyl)-1*H*-indole-3-yl]phenyl)prop-2-enoyl]phenyl}-quinazoline-2,4-dione (IVb):
KBr IR: 3062 (C-H str., Ar-H),1642 (C=O str.), 740 (C-Cl), ^{1}HNMR ($CDCl_3$) δ: 6.4-7.4 (m, 17H, Ar-H),6.2 (*d*, 1H, Ar-CH=CH), 7.4 (*d*, 1H, Ar-CH=CH).

Synthesis of {3-[1-(3-chlorobenzo[b]thiophene-2-carbonyl)-1*H*-indole-3-yl]-4-methoxy phenyl)prop-2-enoyl]phenyl}-quinazoline-2,4-dione (IVc):
KBr IR: 3065 (C-H str., Ar-H),1648 (C=O str.), 745 (C-Cl), ^{1}HNMR ($CDCl_3$) δ: 6.8-7.6 (m, 16H, Ar-H),6.4 (*d*, 1H, Ar-CH=CH), 7.2 (*d*, 1H, Ar-CH=CH), 3.4 (s, 3H OCH3).

Synthesis of {3-[1-(3-chlorobenzo[b]thiophene-2-carbonyl)-1*H*-indole-3-yl]-4-N,N dimethylaminophenyl)prop-2-enoyl]phenyl}-quinazoline-2,4-dione (IVd):
KBr IR: 3055 (C-H str., Ar-H),1664 (C=O str.), 748 (C-Cl), ^{1}HNMR ($CDCl_3$) δ: 6.4-7.3 (m, 16H, Ar-H),6.2 (*d*, 1H, Ar-CH=CH), 7.8 (*d*, 1H, Ar-CH=CH), 3.82 (s, 6H, N(CH3)2).

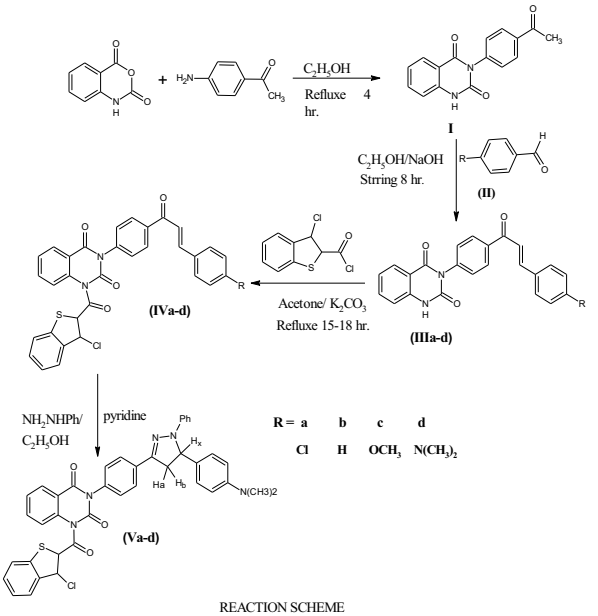
Synthesis of {3-[1-(3-chlorobenzo[b]thiophene-2-carbonyl)-1*H*-indole-3-yl]-4-chlorophenyl)-4,5-dihydro-1H-pyrazol-3-yl]phenyl}-quinazoline-2,4-dione (Va-d):
To a mixture of (**IVa,** 0.01 mole) and phenyl hydrazine (0.01 mole) in absolute alcohol, catalytic amount of pyridine was added and the reaction mixture was refluxed for 8 hrs. After cooling, the reaction mixture was poured slowly into crushed ice with stirring. The solid product obtained was filtered, washed, dried and recrystallized from ethanol.

Compounds **Vb-d** were prepared by similar method with minor change in reaction conditions. Their spectral data are given below:
IR (KBr) cm-1: 3082 (C-H str., Ar-H), 2925 (C-H str., CH2), 1722 (C=O str.), 1590 (C=N str.), 706 (C-S str.), 670 (C-Cl str.) ; 1H NMR (CDCl3) δ (ppm): 8.8-7.4 (m, 21H, Ar-H), 3.36 (dd, 1H, H_a), 3.99 (dd, 1H, H_b), 6.22 (dd, 1H, H_x). MS, m/z: 686.

Synthesis of {3-[1-(3-chlorobenzo[b]thiophene-2-carbonyl)-1*H*-indole-3-yl]phenyl)-4,5-dihydro-1H-pyrazol-3-yl]phenyl}-quinazoline-2,4-dione (Vb):
IR (KBr) cm-1: 3075 (C-H str., Ar-H), 2922 (C-H str., CH2), 1718 (C=O str.), 1565 (C=N str.), 702 (C-S str.), 654 (C-Cl str.) ; 1H NMR (CDCl3) δ (ppm): 8.2-7.3 (m, 22H, Ar-H), 3.32 (dd, 1H, H_a), 3.94 (dd, 1H, H_b), 6.10 (dd, 1H, H_x). MS, m/z: 652.

Synthesis of {3-[1-(3-chlorobenzo[b]thiophene-2-carbonyl)-1*H*-indole-3-yl]-4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-3-yl]phenyl}-quinazoline-2,4-dione (Vc):
IR (KBr) cm-1: 3078 (C-H str., Ar-H), 2927 (C-H str., CH2), 1724 (C=O str.), 1562 (C=N str.), 708 (C-S str.), 634 (C-Cl str.) ; 1H NMR (CDCl3) δ (ppm): 8.6-7.8 (m, 21H, Ar-H), 3.38 (dd, 1H, H_a), 3.98 (dd, 1H, H_b), 6.14 (dd, 1H, H_x), 3.2 (s, 3H OCH3). MS, m/z: 682.

Synthesis of {3-[1-(3-chlorobenzo[b]thiophene-2-carbonyl)-1*H*-indole-3-yl]-4-N,N dimethylaminophenyl)-4,5-dihydro-1H-pyrazol-3-yl]phenyl}-quinazoline-2,4-dione (Vd):
IR (KBr) cm-1: 3074 (C-H str., Ar-H), 2925 (C-H str., CH2), 1723 (C=O str.), 1558 (C=N str.), 712 (C-S str.), 654 (C-Cl str.) ; 1H NMR (CDCl3) δ (ppm): 8.4-7.7 (m, 21H, Ar-H), 3.34 (dd, 1H, H_a), 3.91 (dd, 1H, H_b), 6.18 (dd, 1H, H_x), 2.94 (s, 6H, $N(CH_3)_2$).MS, m/z: 695.



REACTION SCHEME

RESULTS AND DISCUSSION:

The Synthetic route for obtaining the final products is presented in Scheme. The required intermediate 3-(4-acetylphenyl) quinazoline-2,4-dione was prepared by reaction of isatoic anhydride and *p*-aminoacetophenone by refluxing in ethanol. Formation of (I) was confirmed by IR absorption spectra at 1693 cm^{-1} due to carbonyl group. This is further supported by appearance of ^{1}H NMR signal at δ 8.6 for NH group. Compound (I) was converted to chalcones 3-[4-{3-(4-subsituted phenyl) prop-2-enoyl}phenyl] quinazoline-2,4-dione **(IIIa-d)** by treating with corresponding aromatic aldehydes (IIa-d) in NaOH/ethanol. IR and ^{1}H NMR spectral data established the structure of these compounds. IR absorption band at 1648-1665 cm^{-1} indicated the presence of α, β-unsaturated carbonyl functionalities. Compounds **(IIIa-d)** were condensed with 3-chloro-1-benzothiophene-2-carbonyl chloride in acetone presence of K_3CO_3 as a base to furnish {3-[1-(3-chlorobenzo[b]thiophene-2-carbonyl)-1*H*-indole-3-yl]-4-chlorophenyl)prop-2-enoyl]phenyl}-quinazoline-2,4-dione **(IVa-d)**.These Structure was confirmed by disappearance of IR peak for N-H functionality. **(IVa-d)** when treated with $PhNHNH_2$/pyridine, separately, afforded {3-[1-(3-chlorobenzo[b]thiophene-2-carbonyl)-1*H*-indole-3-yl]-4-chlorophenyl)-4,5-dihydro-1H-pyrazol-3-yl]phenyl}-quinazoline-2,4-dione **(Va-d).** The mass spectrum also supported the proposed structure by viewing the molecular ion peak at m/z 686. Physical and analytical data of synthesized compounds are summarized in **Table I**.

Table: 1- physical and analytical data of synthesized compounds:

Compd	Mol. Formula	Mol. Weight	Yield (%)	m.p. (oC)	Found (calcd) % N
1	C16H12N2O3	380	96	86	7.04/7.36
3a	C23H15ClN2O3	402	88	83	6.56/6.96
3b	C23H16N2O3	368	87	79	7.28/7.60
3c	C24H18N2O4	398	91	81	6.75/7.03
3d	C25H21N3O3	411	90	80	9.95/10.21
4a	C32H20ClN2O4S	599	73	100	11.20 (11.31)
4b	C32H21ClN2O4S	565	72	137	9.36 (10.37)
4c	C33H23ClN2O5S	595	70	154	9.37 (10.47)
4d	C34H26ClN3O4S	688	71	87	12.02 (13.52)
5a	C38H23Cl2N4O3S	686	63	265	7.05 (7.42)
5b	C38H24ClN4O3S	652	61	215	5.96 (6.98)
5c	C38H23Cl2N4O3S	682	58	147	6.93 (7.03)
5d	C38H23Cl2N4O3S	695	53	132	8.48 (9.18)

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