Synthesis of substituted quinazolinones

ASSIGN BUSTER

6. DISCUSSION

Heterocyclic compounds, widely distributed in nature are very essential to life. They play a vital role in the metabolism of all living cells. With their high degree of structural diversities and broad spectrum activities, they have proven to be one of the most economically useful chemotherapeutic agents. Synthesis of novel heterocyclic compounds with more potent activities, better efficacy and lower toxicity is the need of the day to the modern synthetic and medicinal chemists.

In the present work, a total of 90 newer therapeutic compounds with heterocyclic rings like quinazolinonyl isoxazole and thiocarbamoyl pyrazolines were synthesized by conventional heating. In the 1^{st} step, a total of 18 substituted quinazolinones were synthesized followed by 18 substituted acetylated quinazolinones in the 2^{nd} step by acetylation of 1^{st} step compounds. Treatment of various substituted acetylated quinazolinones with benzaldehyde lead to 18 substituted quinazolinonyl chalcones respectively. Further, when the chalcones were treated with thiosemicarbazide and $NH_2OH.HCl$ lead to synthesis of a total of 36 compounds with complex quinazolinonyl thiocarbamoyl pyrazolines and quinazolinonyl isoxazoles.

All the above synthesized compounds were structurally confirmed by the IR, ^{1}HNMR and mass spectral analysis. After structural confirmation by physical and spectral characterizations, they were evaluated for pharmacological activities like antibacterial, antifungal, anthelmintic, analgesic and anti-inflammatory activities.

6. 1 Structural characterization of synthesized compounds

Reaction of anthranilic acid and its derivatives bromo, iodo anthranilic acids with aromatic amines (aniline, *p* -chloro aniline, *p* -bromo aniline, *m* -chloro aniline, *p* -fluoro aniline and *p* -methyl aniline) and carbon disulfide in the presence of potassium hydroxide in methanol under reflux for 3hr afforded the corresponding 3-(un)substituted phenyl-6-(un)substituted-2-thioxo-4(3 *H*)-quinazolinones 1a-r. Absorption bands in the range 3210-3445 cm $^{-1}$ and 1505-1590 cm $^{-1}$ in the IR spectrum of the synthesized compounds (1a-r) indicated the presence of N-H and a thioureide group (N-C= S) in the thioxoquinazolinone system. Strong absorption band in the range of 1600-1690 cm $^{-1}$ and a medium band at 1100-1290 cm $^{-1}$ were also observed due to C= O stretching and C= S stretching respectively [66]. The absence of any band in the region 2600-2550 cm $^{-1}$ (characteristic of a thiol group) indicated that the compound exists in the solid state in the thione form. The ^{1} HNMR spectrum of 2-thioxo-quinazolin-4(3 *H*)-one in DMSO-d $_{6}$ showed a singlet of 1H intensity at δ13 ppm for the proton attached to the nitrogen at position 1, and a complex multiplet of 14 protons between δ 6. 0-8. 8 ppm. All the above results correlate and confirm the formation of thioxoquinazolinone ring system in respective compounds 1 a-r.

When compounds 1 a-r treated with acetic anhydride, N-acetylation was took place and acetyl group was introduced at 1 st position of the thioxo quinazolinone nucleus and gave compounds 2 a-r. Acetylation was confirmed by the appearance of peak at δ 1. 72 ppm and disappearance of a peak

corresponding to NH in between δ 9. 7 ppm to δ 13. 0 ppm due to the protons of acetyl group.

Claisen-Schmidt condensation of 2 a-r with benzaldehyde in alcoholic alkali gave corresponding quinazolinonyl chalcones 3 a-r. IR spectrum of the quinazolinonyl chalcones showed a peak at 1670 cm $^{-1}$ characteristic of ï ¡, ï ¢-unsaturated keto functional group [255] of chalcones. Appearance of doublets in the range of δ 6. 7-6. 9 ppm and δ 7. 44-7. 56 ppm, disappearance of singlet corresponds to 3 protons of the N- acetyl group confirmed the 2-propen-1-one moiety of the titled compounds 3 a-r.

5-Phenyl-3-[3 ′ -(un) substituted phenyl-6’-(un) substituted-2 ′ -thioxo-4 ′ (3 ′ *H*)-quinazolinon-1 ′ -yl]-1-thiocarbamoyl-2-pyrazolines 4 a-r were prepared by refluxing quinazolinonyl chalcones with thiosemicarbazide in the presence of sodium hydroxide. Disappears of peck corresponds to α, β-unsaturated keto functional group of chalcones at 1670 cm $^{-1}$ and appearance of pecks at 709. 92 cm $^{-1}$, 1067. 42 cm $^{-1}$, 1386. 89 cm $^{-1}$, 1517 cm $^{-1}$ and 3239. 62 cm $^{-1}$ confirmed the thiocarbamoyl-2-pyrazoline nucleus. Appearance of singlet at δ 8. 46 ppm indicated the two protons of thiocarbamoyl group (NH $_2$ -C= S) at 1 st position of 1-thiocarbamoyl-2-pyrazoline ring [256].

Cycloaddition of chalcones with hydroxyl amine hydrochloride (NH $_2$ OH. HCl) gave isoxazoles 5 a-r. Absence of C= O band and appearance of new bands in the range of 1210-1270 cm $^{-1}$, 1560-1610 cm $^{-1}$ in the IR spectrum of all the compounds indicated -C-O-N- and C= N of isoxazole ring respectively [257, 258]. Appearance of a peek in the range of δ 5. 9-6. 9 ppm in ^{1} HNMR

spectrum correlates with IR spectrum data and confirms the formation of isoxazole ring in the respective compounds.

6. 2 Biological activities

6. 2. 1 Antibacterial activity

All the titled compounds (1 a-r, 2 a-r, 3 a-r, 4 a-r and 5 a-r) were evaluated for antibacterial activity. The results were given in Table 5. 29, 5. 30, 5. 31, 5. 32 and 5. 33. In all compounds basic skeleton and the electron withdrawing halogens played a key role in pharmacological activities. Compounds with electron withdrawing F, Br, Cl groups at para position of phenyl ring and electron releasing CH_3 group at para position of the phenyl ring displayed maximum activity against *Bacillus subtilis*

6. 2. 2 Antifungal activity

All the titled compounds (1 a-r, 2 a-r, 3 a-r, 4 a-r and 5 a-r) were evaluated for antifungal activity. The results were given in Table 5. 34, 5. 35, 5. 36, 5. 37 and 5. 38. In all compounds basic skeleton and the electron withdrawing halogens played a key role in pharmacological activities. Compounds with electron withdrawing F, Br, Cl groups at para position of phenyl ring and electron releasing CH_3 group at para position of the phenyl ring displayed maximum activity against Candida species.

6. 2. 3 Anthelmintic activity

All the titled compounds (1 a-r, 2 a-r, 3 a-r, 4 a-r and 5 a-r) were evaluated for anthelmintic activity. The results were given in fig 5. 1, 5. 2, 5. 3, 5. 4 and

5. 5. In all compounds basic skeleton and the electron withdrawing halogens played a key role in pharmacological activities. Compounds with electron withdrawing F, Br, Cl groups at para position of phenyl ring and electron releasing CH_3 group at para position of the phenyl ring displayed maximum activity against Perithima *posthuma.*

6. 2. 4 Analgesic activity

All the titled compounds (1 a-r, 2 a-r, 3 a-r, 4 a-r and 5 a-r) were evaluated for analgesic activity. The results were given in fig 5. 6, 5. 7, 5. 8, 5. 9 and 5. 10. In all compounds basic skeleton and the electron withdrawing halogens played a key role in pharmacological activities. Compounds with electron withdrawing F, Br, Cl groups at para position of phenyl ring and electron releasing CH_3 group at para position of the phenyl ring displayed potent analgesic activity.

6. 2. 5 Anti-inflammatory activity

All the titled compounds (1 a-r, 2 a-r, 3 a-r, 4 a-r and 5 a-r) were evaluated for anti-inflammatory activity. The results were given in fig 5. 11, 5. 12, 5. 13, 5. 14 and 5. 15. In all compounds basic skeleton and the electron withdrawing halogens played a key role in pharmacological activities. Compounds with electron withdrawing F, Br, Cl groups at para position of phenyl ring and electron releasing CH_3 group at para position of the phenyl ring displayed maximum anti inflammatory activity.