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# A Review on synthesis and biological profiles of some Quinazolines and (4*H*)-3,1-Quinazolin-4-ones of active substituents and their uses as starting materials in reaction schemes

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**ABSTRACT**

Variety of quinazolines and quinazolinones have been considered as precursors for many novel derivatives depending on type and position of the active substituent(s) they have. A review on the synthesis of some quinazolines and quinazolinones having substituent(s) at 2-, 3-, and 4-positions and their uses as starting materials in the synthesis of novel derivatives have been introduced. Also, their reactions and their dependence on the reaction reagents and/or reaction condition have been discussed. In addition, their role in producing derivatives of valuable biological importance has also been surveyed.



## 1. Introduction

In recent years, there has been an increasing interest in the chemistry of 4(3*H*)-quinazolinones because of the biological importance they have. Many of them show antifungal (Bartroli *et al.,* 1998), antibacterial (Shiba *et al* 1997), anticancer (Abdel-Hamid *et al* 1997), anti-inflammatory (Barker 1995), anticonvulsant (Bekhit *et al* 1998), immunotropic (Gursoy *et al.,* 1995), hypolipidemic (Nawrocka *et al.,* 1997), antitumor (Kurogi *et al.,* 1996), antiulcer (Hame *et al.,* 1996), analgesic (Terashima *et al.,* 1995), anti-proliferative activities (Raffa *et al.,* 1999) and inhibitory effects for thymidylate synthase enzyme (Baek *et al.,* 1998) and poly (ADP-ribose) polymerase (PARP) (Griffin *et al.,* 1998). The 4 (3*H*)-quinazolinones can act as semi-cyclic amides or iminols, due to the tautomer phenomenon they have. Their reactions in either form with alkyl or acyl halides are perhaps the most interesting due to the large number of the heterocycles that are obtained either directly or through further transformations of the initially formed products. In addition, quinazolines are a big family of heterocyclic compounds, which have shown broad variety of biological activity profiles (Jhone 1982; Brown 1996), e.g. analgesic, narcotic, diuretic, antihypertensive, anti-malarial, sedative, hypo-glycaemic, antibiotic, anti-tumoral and many others. It has been found that the biological activity strongly depends on the type and place of the substituent in the molecule (Armarego 1967). Out of the wide substitution patterns known, 4-aminoquinazolines are useful as fungicides (Nakagami *et al.,* 1982; Haley 1994), anti-inflammatory (Palanki *et al.,* 1999;, Myers *et al.,* 1998), anticancer (Baker 1999), anti-microbial and anti-hypertensive agents (Nauta 1976; Mizogami *et al.,* 1986). Some 4-anilinoquinazolines were found to be potential and highly selective inhibitors of human immunoglobulin E (Berger *et al.,* 2001) and epidermal growth factor receptor tyrosine kinase (Bridges 2001) which regulates the cell growth and proliferation, so they work as potent anti-allergic or anticancer agents, respectively. It is well known that quinazolin-4-one has three isomeric forms (**a-c**). Only **a** and **b** are tautomers (Fig. 1).

Considering tautomer forms a and b, the substitution on the hetero-ring can be sub-classified into two categories and therefore results in the formation of either the 2,3-disubstituted quinazolin-4-one or the 2,4-disubstituted quinazoline. However, in the benzene-ring moiety of both forms, four positions are possible, the 5-, 6-, 7-, and 8- positions (Fig. 2).

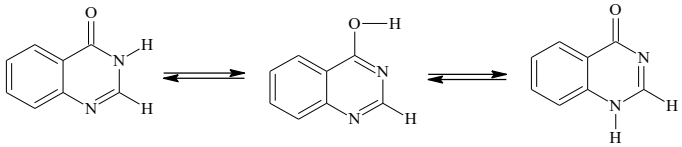


**Fig. 1.** Tautomers and isomers of quinazolin-4-one

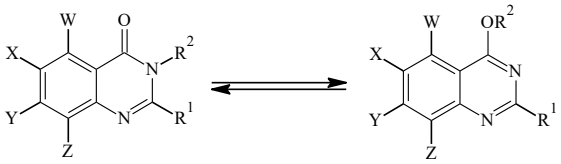


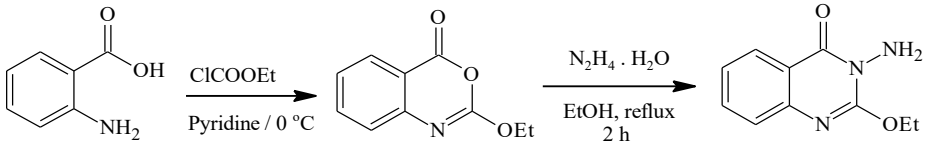
**Fig. 2**. Possible substituent position on the quinazoline and quinazolinone structures

Throughout our current review, any substituent on the hetero-ring moiety ($R^1$ and $R^2$) at positions 2-, 3-, and 4- can have an important contributing role to the QSAR either from the synthetic approach and/or the biological significance. This was indicated by the type of substituent(s) which can either be a chemically active group(s) that can make the whole compound a reactive nucleus used to start a new reaction scheme or an inactive group that makes the compound an end product. The active group that can make the compound useful in synthesis of novel derivatives can itself be classified according to the type of atoms composing its chemical formula.

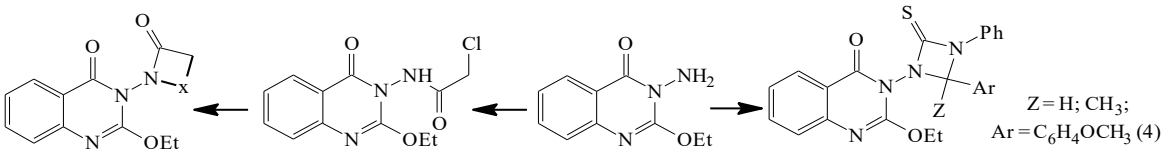
## 2. Reaction Schemes

Starting a reaction scheme with a derivative containing an active substituent imposes a specific method of preparation for that derivative, depending on type and site of substituent. For

example, a scheme for the 3-amino derivative of quinazolin-4-one requires the preparation of benzoxazin-4-one as a first step followed by addition of hydrazine hydrate to get the 3-amino-derivative according to the following reaction (El-Hashash *et al.*, 2011) (Scheme. 1).



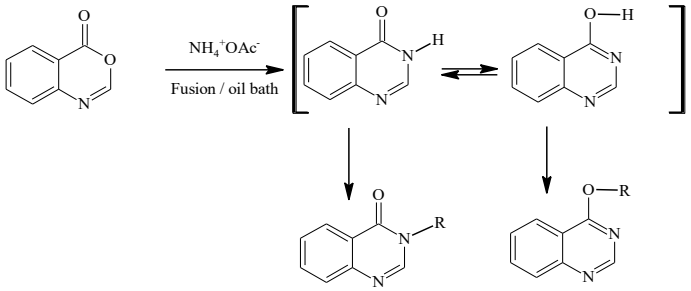

**Scheme 1.** Preparation of a 3-aminoquinazoli-4-one derivative




X = -$COCH_2S$-; -$COCH_2NH$-; -$CH_2CH_2NH$-; -C(NH)-O-; -CO-O-; -CO-S-; -C(NH)-CH(R)-; R = CN, COOEt.

-$CH_2CH_2NR'$- where R' = p-acetylaminobenzenesulfonyl; -$CH_2CH_2NR'$- where R' = p-acetylaminobenzenesulfony

**Scheme 2.** The 3-aminoderivative of quinazolinone as a starting material



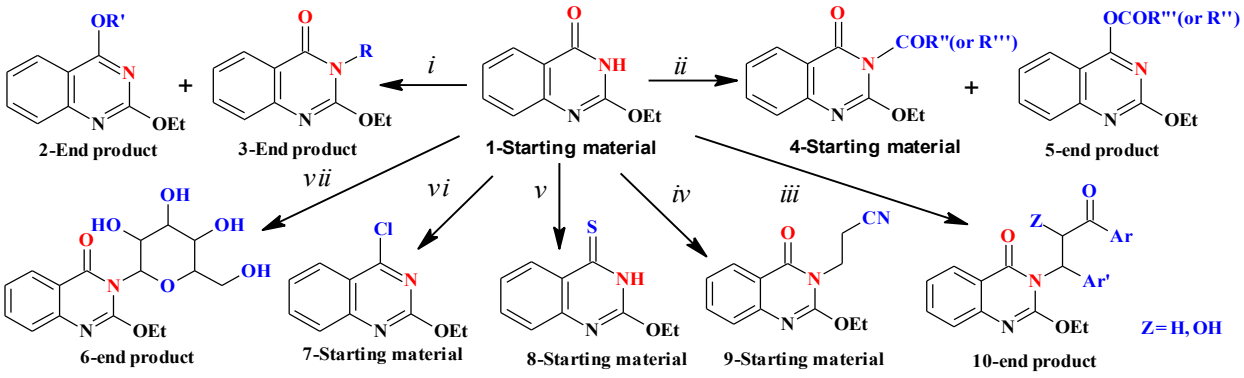

**Scheme 3.** Preparation and Reaction of the quinazolin-4-one derivative

## 3. Types of Reaction Products

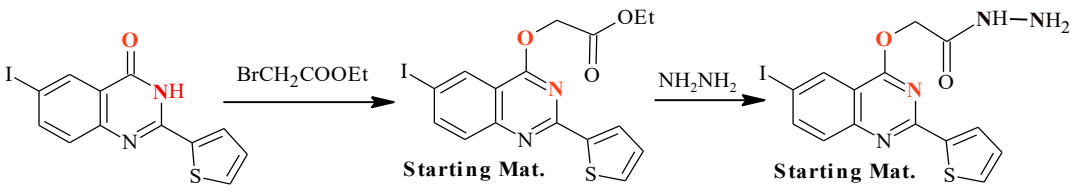
A reaction product can itself be either a final product that can no longer be useful in starting a new reaction scheme or a new starting material for a new reaction scheme. For example, the 3-amino derivative in Scheme 1 can be used as a starting material for synthesizing other derivatives according to the following (Scheme 2) (El-Hashash *et al* 2011).

On the other hand, the benzoxazin-4-one product in scheme 1 can be used (Scheme 3) in the preparation of quinazolin-4-one derivative itself (El-Hashash *et al* 2012). In Fact, the hydrogen atom is the most important component of the active amide group or hydroxyl group. In addition, the position of the mentioned groups at the ring also reveals the compound importance. Depending on the reaction condition, the substitution occurs either on the amidic hydrogen at 3-position or the enolic hydrogen at 4-position.

The contributing recent research revealed the selectivity of reaction in choosing the product either as a reaction end product or a new reaction starting material depending on the reagent used and reaction condition (El-Hashash *et al.*, 2012, El-Azab *et al.*, 2013). The following reaction scheme (Scheme 4) shows the difference between end products and starting materials.




(i) RX = alkyl halide, R'X = allyl halide / dry acetone; (ii) R", R"' = acyl, aroyl, heteroaroyl halides / solvent dependent; (iii) chalcone or its oxide / EtOH; (iv) acrylonitrile / DMF; (v) $P_2S_5$ / xylene; (vi) $POCl_3$ / $PCl_5$ ; (vii) alpha-bromoglucose / $CH_3CN$

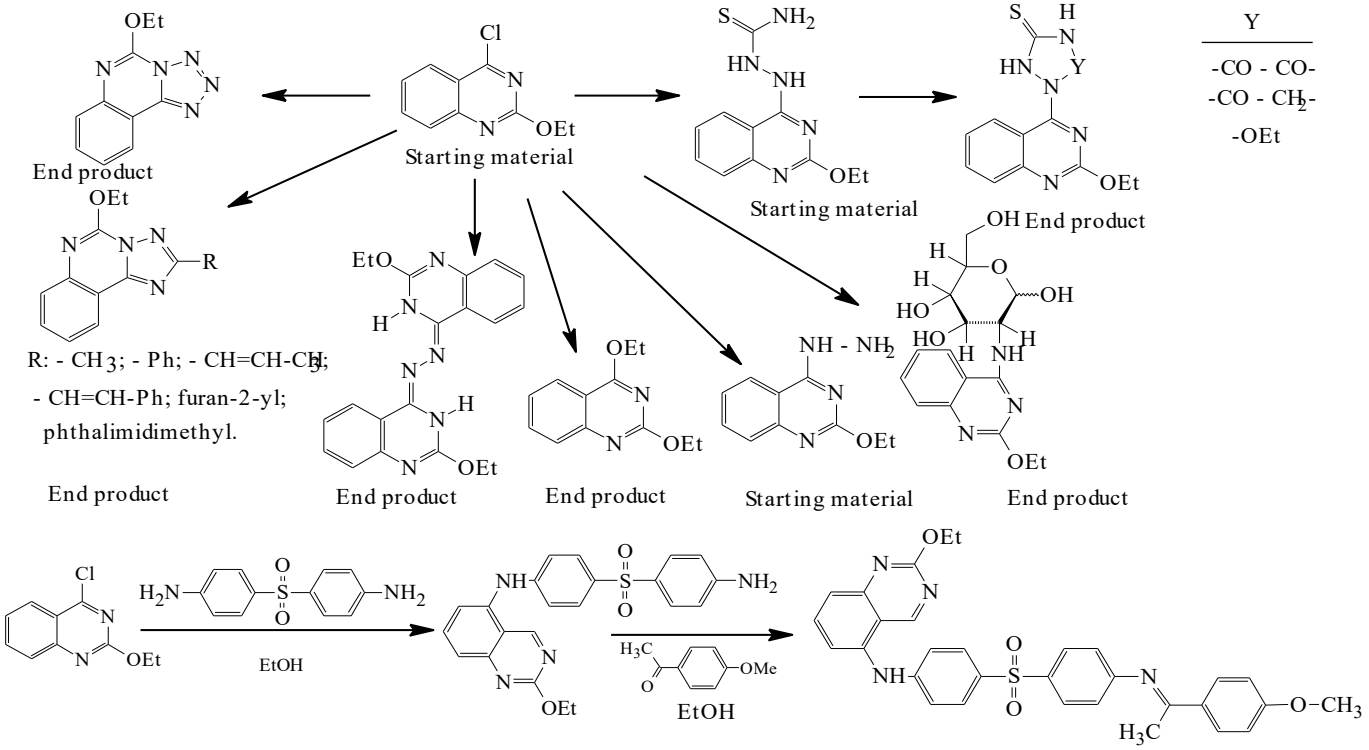



**Scheme 4**. Synthetic Pathways of starting materials and end products from quinazolin-4-one

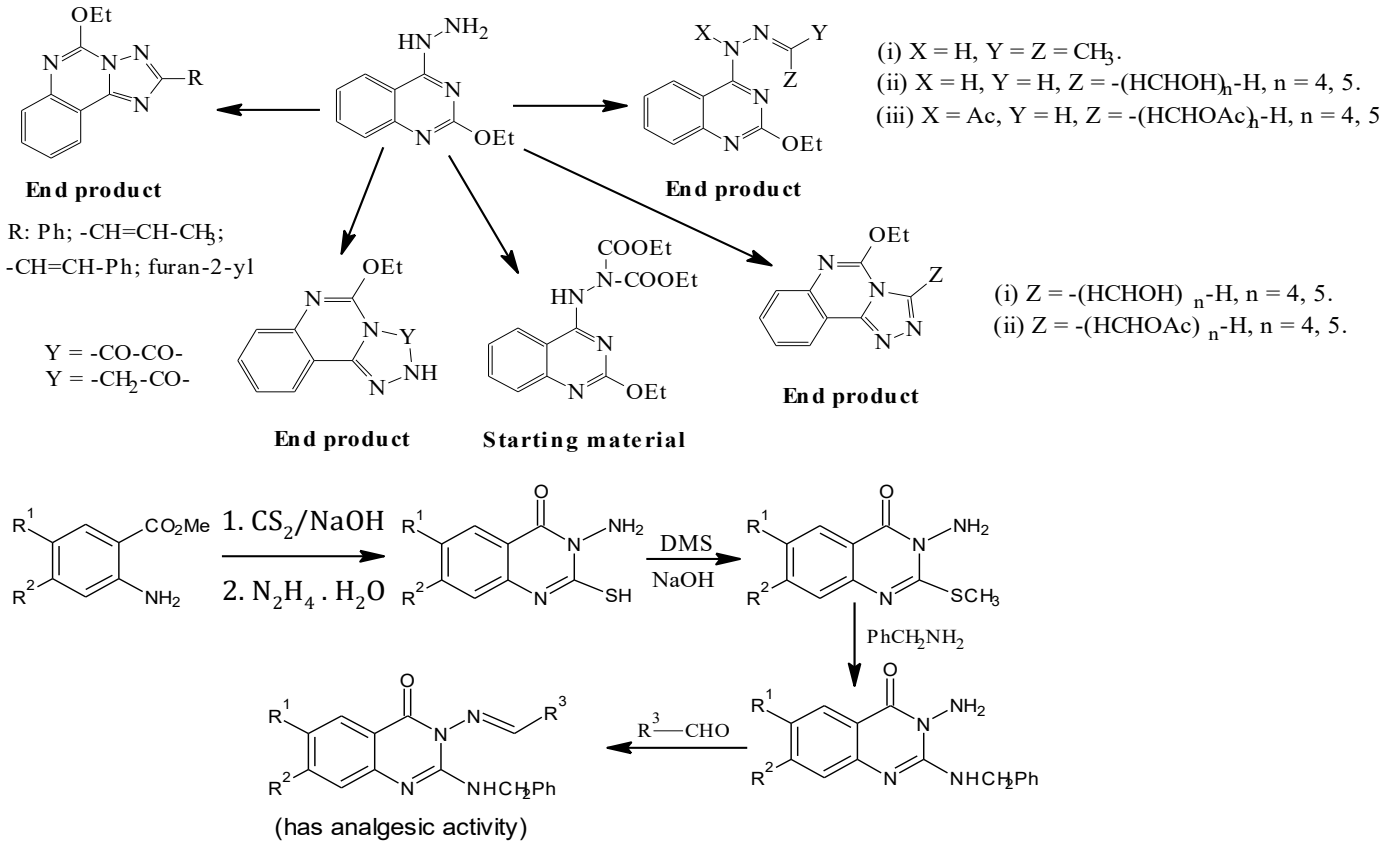
According to Scheme 4, there are six starting materials, most of them derived from the 2-ethoxyquinazolinone.

Among the broad synthetic pathways for the 4-amino quinazoline preparations, the substitution of chlorine atom in 4-chloroquinazolines by amino group is the shortest and cheapest (Katritzky *et al.,* 1996 and Katritzky *et al.,* 2000). The 4-chloroderivative could also be used to start completely different preparations (Scheme 5) (El-Hashash *et al.,* 2011, Darwish 2011).

In a similar manner, the 4-hydrazinoquinazoline and 4-thiosemicarbazido derivatives were used to start further new scheme, mainly ring closure reactions (El-Hashash *et al.,* 2012), some showed analgesic activity (Scheme 6) (Ayyad *et al.,* 2016).



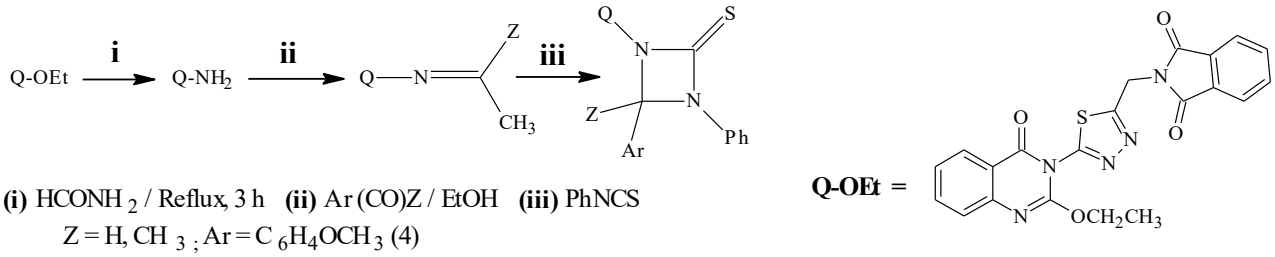

**Scheme 5.** Schematic representation for the 4-chloroquinazoline reactions



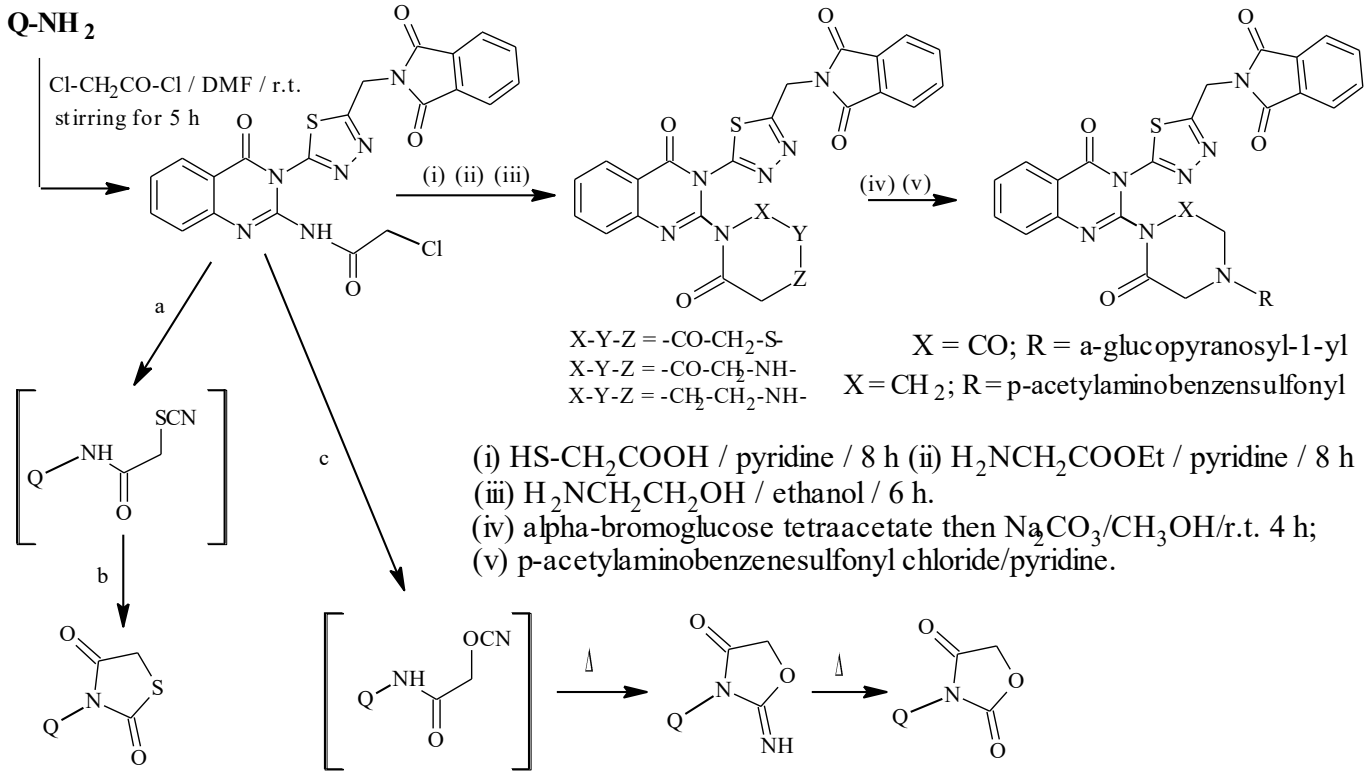

**Scheme 6.** Schematic representation for the 4-hydrazinoquinazoline reaction

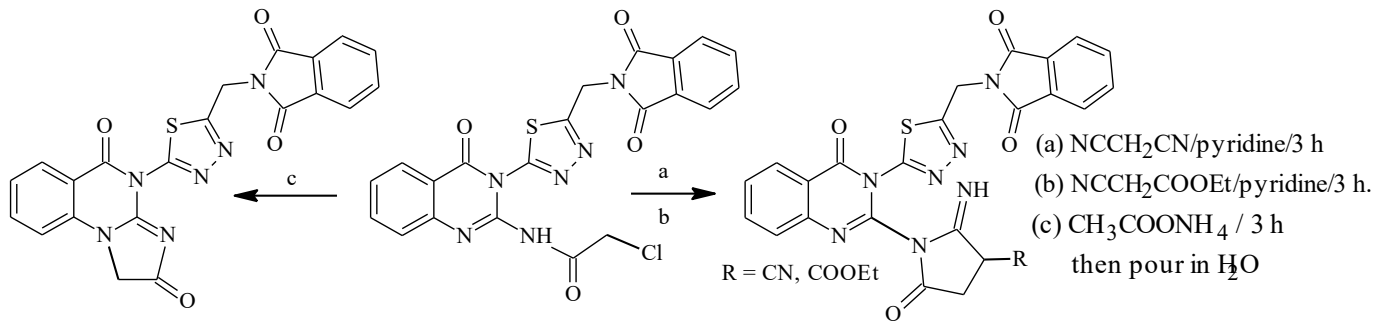
On the other hand, the 2-amino quinazolin-4-one derivative had a remarkable role with the 3-position being blocked with an inactive substituent (El-Hashash *et al.*, 2011) (Scheme 7).

In another route, the 2-amino derivative when reacted with chloroacetyl chloride gave a new staring material (Darwish 2011) (Scheme 8).




**Scheme 7.** Synthetic pathways and reactions of the 2-amino derivative



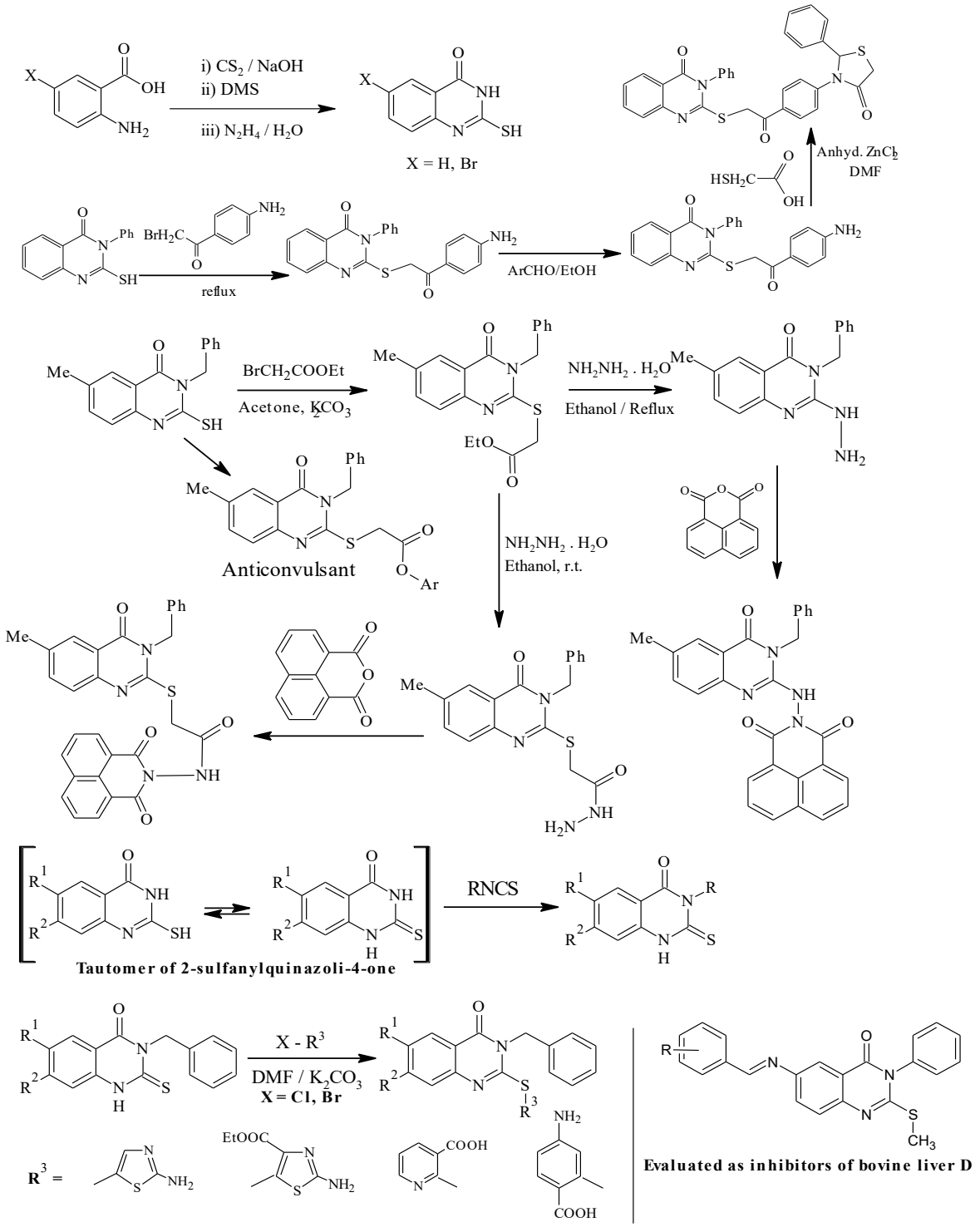




**Scheme 8.** Synthetic pathway and reactions of the 2-chloroacetylaminoderivative

Recently, newly synthesized novel 2-sulfanylquinazolin-4-one derivatives have been used as starting materials. Some of them gave end products of antibacterial, antifungal, anticonvulsant activity and as inhibitors of bovine liver DHFR (El-Azab *et al.*, 2013; Darwish 2011; Shailaja *et al.*, 2013; Al-Omary *et al.*, 2013; Abdel Hamid *et al.*, 2001; Al-Omar *et al.*, 2004; Dave *et al.*, 2015; El-Helby *et al.*, 2003) (Scheme 9).

## 4. Coclusion

In variety of reactions there is almost a chance to start new schemes with new starting materials and new methods for further material synthesis. This can help in invention of novel derivatives. This does not necessarily means lowering the value of end products.




**Scheme 9.** Possible reaction scheme for a 2-sulfanylquinazolin-4-one derivative

## References


Abdel Hamid, S.G.; El-Obaid, H.A.; Al-Majed, A.A.; El-Kashef, H.A.; El-Subbagh, H.I. (2001) 'Synthesis and anticonvulsant activity of some new 4-oxo-3H-quinazoline analogs', *Med. Chem. Res.*, 10, pp. 378–389.

Abdel-Hamid, S.G. (1997) 'Synthesis of some New Heterocyclic Systems Bearing 2-Phenyl-6-iodo-4-(3*H*)-quinazolinon-3-yl Moiety as Antibacterial Agents', *J. Ind. Chem. Soc.*, 74, pp. 613-618.

Al-Omar, M.A., Abdel Hamide, S.G., Al-Khamees, H.A.' El-Subbagh, H.I. (2004) 'Synthesis and biological screening of some new substituted (3*H*)quinazolin-4-one analogues as antimicrobial agents', *Saudi Pharm. J.*, 12, pp. 63–71.

Al-Omary F.A.M, Hassan Gh.S., El-Messery Sh.M., Nagi M.N., Habib El.E., El-Subbagh H.I. (2013) 'Non classical antifolates, part 3: Synthesis, biological evaluation and molecular modeling study of some new 2-heteroarylthio-quinazolin-4-ones', *European Journal of Medicinal Chemistry*, 63, pp. 33-45.

Armarego, W. (1967) *Fused Pyrimidines: Part I - Quinazolines*, Interscience Publishers: New York– London –Sydney.

Ayyad, R.A.; Sakr, H.M.; El-Gamal, K.M. (2016) 'Design, Synthesis, Computer Modeling and Analgesic Activity of Some New Disubstituted Quinazolin-4(3*H*)-ones', *Med. Chem.*, 6(5), pp. 299-305.

Baek, D.J., Park, Y.K., Heo, H.I., Lee, M.H., Yang, Z.Y. &Chio, M.H. (1998) 'Synthesis of 5-substituted quinazolinone derivatives

and their inhibitory activity *in vitro*', *Bioorg. Med. Chem. Lett.*, 8, pp. 3287-3290.

Baker, A.J. (1999) US Patent 5932574.

Baker, A.J. (1999) US Patent 5942514.

Barker, A. (1995) 'Preparation of 4-Anilinoquinazolines as Anticancer Agents', *J. Eur. Pat.*, 635498, *Chem. Abstr.*, *122*, pp. 214099.

Bartroli, J., Turmo, E., Alguero, M., Boncompte, E., Vericat, M.L., Coute, L., Ramis, J., Merlos, M.,Garcia-Rafanell, J. & Forn, J. (1998) ' New Azole Antifungals. 3. Synthesis and Antifungal Activityof 3-Substituted-4(3*H*)- quinazolinones', *J. Med. Chem.,* 41, pp. 1869-82.

Bekhit, A.A. & Khalil, M.A. (1998) 'A Non-steroidal Anti-inflammatory Agents: Synthesis of Novel Benzopyrazolyl and Quinazolinyl Derivatives of 4(3*H*)-Quinazolinones', *Pharmazie*, 53, pp. 539-543.

Berger, M., Albrecht, B., Breces, A., Neruda, W. &Woisetschläger, M. (2001) '*S*(+)-4-(1-Phenylethylamino)quinazolines as Inhibitors of Human Immunoglobuline E Synthesis: Potency is dictated by stereochemistry and atomic point charges at N-1', *J. Med. Chem.*, 44, pp. 3031.

Bridges, A.J. {2001) 'Chemical inhibitors of protein kinases', Chem. Rev., 101, pp. 2541.

Brown, D.J. (1996) *The Chemistry of Heterocyclic Compounds*, J. Wiley & Sons: New York.

Darwish, K.M. (2011) 'A Facile Synthesis of 4-[(4-{[(1*E*)-1-(4-methoxyphenyl) ethylidene] amino} phenyl)sulfonyl]-*N*-(2-ethoxyquinazolin-4-yl) -*N*-(2-furoyl)aniline', *International Journal of Chemical Science and Technology*, 1, pp. 168-170.

Darwish, K.M. (2011) 'Use of 5-[2-Ethoxyquinazolin-4-one-3-yl]-2-phthalimidomethyl thiadiazole in the Synthesis of *N*- and *C*-Glycosides via Amadori Rearrangement', *Chemistry and Materials Research*, 1, pp. 8-11.

Dave, V.B.; Thakor, M.K. (2015) 'Design, Synthesis and Antimicrobial Activity of Some Newer 3(*H*)-Quinazolin-4-one Derivative', *J. Curr. Chem. Pharm. Sc.*, 5(3), pp. 99-104.

El-Azab, A.S., Abdel-Hamide, S.G., Sayed-Ahmed, M.M., Hassan, Gh.S., El-Hadiyah, T.M., Al-Shabanah, O.A., Al- Deeb, O.A., El-Subbagh, H.I. (2013) 'Novel 4(3*H*)-quinazolinone analogs: synthesis and anticonvulsant Activity', *Medicinal Chemistry Research*, 22, pp. 2815-2827.

El-Hashash, M.A., Darwish, K.M., Rizk, S.A. & El-Bassiouny, F.A. (2011) 'Reactivity of 3-Amino-2-Ethoxyquinazolin-4(3*H*)-one in the Synthesis of Novel Quinazolinone Derivatives', *International Journal of Chemical Science and Technology,* 1, pp. 141-149.

El-Hashash, M.A., Darwish, K.M., Rizk, S.A. & El-Bassiouny, F.A. (2012) 'Use of 2-Ethoxy(4*H*)-3,1-benzoxazin-4-one as a Precursor for Synthesis of Quinazoline and Quinazolinone Starting Materials', *Chemical and Process Engineering Research*, 2, pp. 17-32.

El-Hashash, M.A., Darwish, K.M., Rizk, S.A. & El-Bassiouny, F.A. (2012) 'Uses of 2-Ethoxy-4(3*H*) quinazolinone in Synthesis of Quinazoline and Quinazolinone Derivatives of Antimicrobial Activity: The Solvent Effect', *Global Journal of Health Science,* 4, pp. 162-173.

El-Hashash, M.A., Darwish, K.M., Rizk, S.A. & El-Bassiouny, F.A. (2011) 'The Reactivity of 2-Ethoxy-4-Chloroquinazoline and Its Use in Synthesis of Novel Quinazoline Derivatives', *Organic Chemistry International*, pp. 1-7.

El-Hashash, M.A., Darwish, K.M., Rizk, S.A. & El-Bassiouny, F.A. (2012) 'Reactivity of 2-Ethoxyquinazolin- 4-yl hydrazine and its Use in Synthesis of Novel Quinazoline Derivatives of Antimicrobial Activity", *Global Journal of Health Science,* 4, pp. 174-183.

El-Hashash, M.A., Darwish, K.M., Rizk, S.A. & El-Bassiouny, F.A. (2011) 'Use of 2-{[5-(2-Amino-4-oxoquinazolin-3(4*H*)-yl)-1,3,4-thiadiazol-2-yl]methyl}-1*H*-isoindole-1,3(2*H*)-dione in the Synthesis of Novel Quinazolinone Derivatives', *Chemical and Process Engineering Research*, 1, pp. 1-9.

El-Hashash, M.A., Darwish, K.M., Rizk, S.A. and El-Bassiouny, F.A. (2011) 'The Uses of 2-Ethoxy(4*H*)-3,1-benzoxazin-4-one in the Synthesis of Some Quinazolinone Derivatives of Antimicrobial Activity', *Pharmaceuticals*, 4, pp. 1032-1051.

El-Helby, A.A.; Abdel Wahab, M.H. (2003) 'Design and synthesis of some new derivatives of3*H*-quinazolin-4-one with promising anticonvulsant activity', *Acta Pharm.*, 53, pp. 127-138.

Griffin, R.J., Srinivasan, S., Bowman, K., Calvert, A.H., Curtin, N.J., Newell, D.R., Pemberton, L.C., Golding, B.T. (1998) 'Resistance-modifying agents. 5. Synthesis and biological properties of quinazolinone inhibitors of the DNA repair enzyme poly(ADP-ribose) polymerase (PARP)', *J. Med. Chem.*, 41, pp. 5247-5256.

Gursoy, A. and Karali, N. (1995) 'Synthesis and Anticonvulsant Activity of New Acyl thiosemicarbazides and Thiazolidones', *Pharmaco.*, 50, pp. 857-866.

Haley, G.J. (1994) US Patent 5373011.

Hame E., Lin C.M., Plowman, J., Wang, H.K., Lee, K.H. & Paull, K.D. (1996) 'Antitumor 2,3-dihydro-2-(aryl)-4(1*H*)-quinazolinone derivatives: Interactions with tubulin', *Biochem. Pharmacol.*, 51, pp. 53-59.

Johne, S. (1982) In *Progress in Drug Research*. In: 'Search for Pharmaceutically Interesting Quinazoline Derivatives: Efforts and Results (1969-1980)', ed. Jucker, E., Ed.; Birkauser Verlag: Basel, 26, pp. 259-341.

Katritzky, A.R.; Pozharski, A.F. (2000) '*Handbook of Heterocyclic Chemistry*, 2nd Edn.', Pergamon: New York.

Katritzky, A.R.; Rees, C.W. (1996) '*Comprehensive Heterocyclic Chemistry II*, Eds', Pergamon Press: Oxford.

Kurogi, Y., Inoue, Y., Tsutsumi, K., Nakamura, S., Nagao, K., Yoshitsugu, H. &Tsuda, Y. (1996) 'Synthesis and hypolipidemic activities of novel 2-[4-[diethoxyphosphoryl) methyl]phenyl] quinazolines and 4(3*H*)- Quinazolinones', *J. Med. Chem.*,*39*(7), pp. 1433-1437.

Mizogami, S., Hiranuma, H., Sekiya, T., Hanazuka, M.(1986) US Patent 4607034.

Myers, M.R., Spada, A; Maguire, M, Persons, P, Zilberstein, A, Hsu, C-Y-J, Johnson, S E (1998) US Patent 5714493.

Nakagami, K.; Yokoi, S.; Nishimura, K.; Nagai, S.; Honda, T.; Oda, K.; Kobayashi, R.; Kojima, M. (1982) US Patent 4323680.

Nauta, W.T. (1976) US Patent 3980650.

Nawrocka, W. and Zimecki, M. (1997) 'Syntheses of novel 3-amino-2(1*H*)-thioxo-4(3*H*)-quinazolinones and evaluation of their immunotropic activity. Part III', *Arch. Pharm.*, 330, pp. 399-405.

Palanki, M.; Suto, M. (1999) US Patent 5939421.

Raffa, D., Dailone, G., Maggio, B., Sehillaci, D. & Plescia, F. (1999) 'Synthesis and Antiproliferative Activity of Novel 3-(Indazol-3-yl)-quinazolin-4(3*H*)-one and 3-(Indazol-3-yl-benzotriazin-4(3*H*)-one Derivatives', *Arch. Pharm.*, 332, pp. 317-320.

Shailaja K.M., Dipukakoty, Shivakumar B., Jayachandran E., .Sreenivasa G.M, Sriranga T. (2013) 'Synthesis and Characterization of Noval Heterocyclic Compounds', *Research and Reviews: Journal of Chemistry*, 2, pp. 40-43.

Shiba, S.A.; El-Khamry, A.A.; Shaban, M.E.; Atia, K.S. (1997) 'ChemInform Abstract: Synthesis and Antimicrobial activity of Some Bis-quinazoline Derivatives', *Pharmazie*, 52, pp. 189-194.

Terashima, K., Shimamura, H., Kawase, A., Tanaka, Y., Tanimura, T., Kamisaki, T., Ishizuka, Y. Sato, M. (1995) 'Studies on Antiulcer Agents. IV. Antiulcer Effects of 2-Benzylthio-5,6,7,8-tetrahydro-4(3*H*)-quinazolinones and Related Compounds', *Chem. Pharm. Bull.*, 43, pp. 2021-2023.