ISOQUINOLINE DERIVATIVES AS CASPASE 3 INHIBITORS-A REVIEW

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ABSTRACT

Our study is to investigate the inhibition of apoptosis or program cell death by blocking the activation of Caspase 3. Caspase 3 belongs to the cysteine-aspartic acid protease (caspase) family. It is encoded by the CASP3 gene. Caspase-3 initiates apoptotic DNA fragmentation by proteolytically inactivating Intracellular Cell Adhesion Molecule. Induction of apoptosis *via* death receptors typically results in the activation of an initiator Caspase such as Caspase 8 or Caspase 10. These Caspases can then activate other Caspases in a cascade. This cascade eventually leads to the activation of the effector Caspases, such as Caspase 3 and Caspase 6. These Caspases are responsible for the cleavage of the key cellular proteins, such as cytoskeleton proteins, that leads to the typical morphological changes observed in cells undergoing apoptosis. There are several anti apoptic drugs present which inhibit apoptosis by several pathways. Isoquinoline 1,3,4-trione could be used for the blocking of activation of Caspase 3. Thus synthesis of isoquinoline 1,3,4-trione & its derivatives could be done. The compound has anti-apoptosis property, thus it has also anti inflammatory action, because during apoptosis inflammation takes place.

APOPTOSIS

Apoptosis occurs in a well-choreographed sequence of morphological events. This process usually starts with the blebbing of the plasma membrane, which breaks up into membrane-enclosed particles, termed apoptotic bodies, containing intact organelles as well as portions of the nucleus. In fact the word 'apoptosis' comes from the ancient Greek, meaning 'falling off ' (of petals from a flower) and refers to the morphological feature of the formation of apoptotic bodies [1]. These apoptotic bodies are rapidly recognized, ingested and eaten by professional phagocytes or neighbouring cells. Under physiological conditions certain modifications occur in the

plasma membrane which function as 'eat-me' signals and enable the apoptotic bodies to be recognized by phagocytic cells. Since the apoptotic bodies are surrounded by an intact plasma membrane, apoptosis usually occurs without any leakage of cellular contents and therefore without provoking an inflammatory response. Moreover, the engulfment of apoptotic cells by macrophages triggers the production of anti-inflammatory cytokines. Because apoptotic cells are eaten and digested so quickly, there are usually few dead cells to be seen in tissue sections, even when large numbers of cells have died. This probably explains why apoptosis was neglected by pathologists for a long time. Looking inside the cell, one of the most noticeable features of apoptosis is the condensation of the nucleus and its fragmentation into smaller pieces, a highly distinctive event that is not seen in other forms of cell death. Another defining feature is the extensive hydrolysis of nuclear DNA into internucleosomal fragments (Fig. 1).

Apoptosis is the major cell death pathway for removing unwanted and harmful cells in a clean or silent manner during embryonic development, tissue homeostasis and immune regulation. In addition, most anti-cancer therapies rely on the activation of apoptotic pathways. As the alterations of apoptosis are stereotypical and similar in all cell types irrespective of the death stimulus, the biochemical mechanisms underlying these changes also follow a similar built-in program. In nematodes, insects and human cells, most, if not all, morphological alterations of apoptosis are mediated by the activation of an evolutionarily conserved and unique class of intracellular proteases known as Caspase [2].

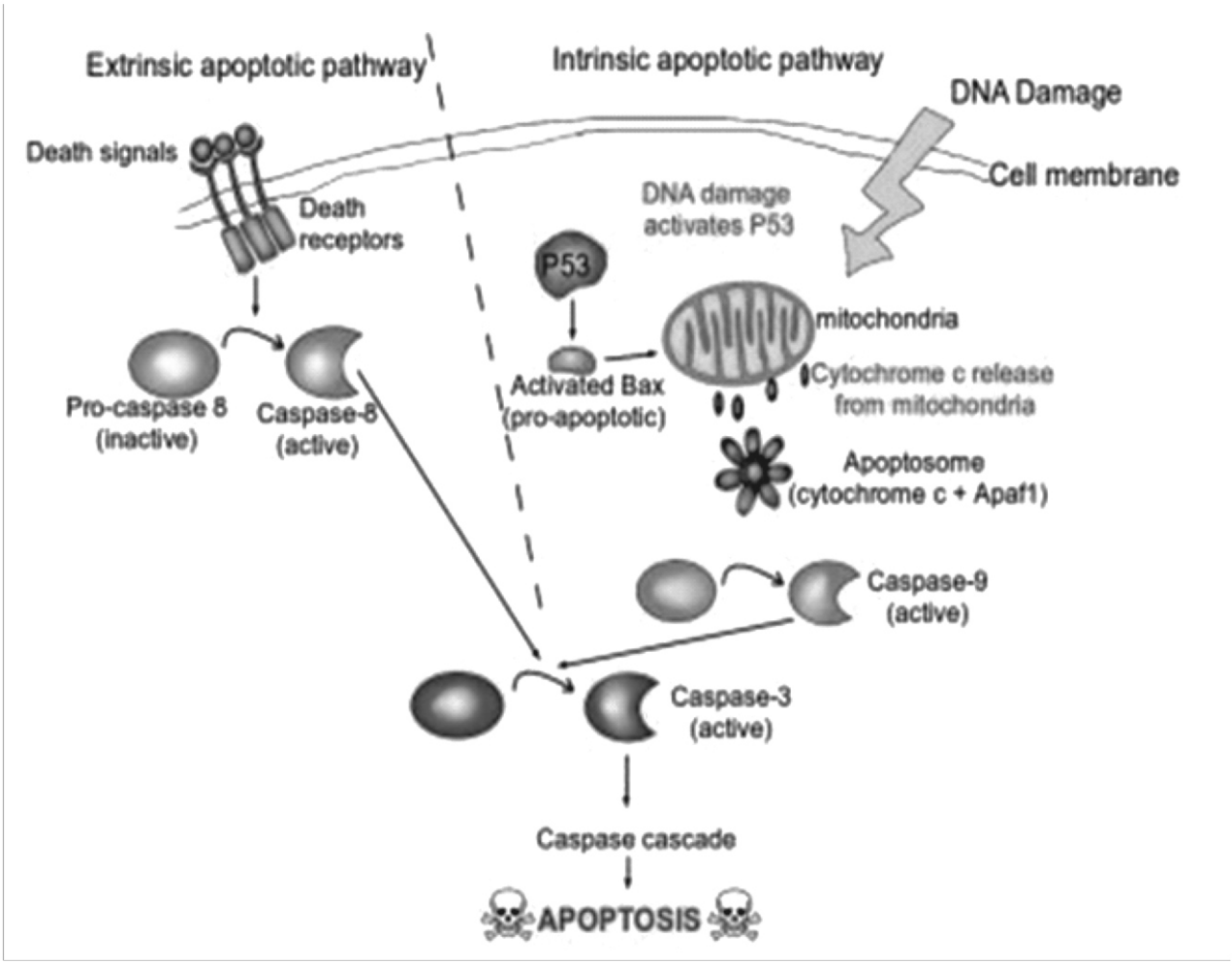

Figure 1: Mechanism of apoptosis

The above picture depicts a brief overview of the extrinsic and intrinsic apoptotic pathways. In the extrinsic pathway, death signals from the surrounding environment of the cell bind to death receptors on the surface of the cell membrane. This causes the conversion of inactive pro-Caspase-8 into active Caspase-8. Caspase-8 then goes on to activate Caspase-3, which begins the Caspase cascade that leads to apoptosis. In the intrinsic pathway, typically initiated by DNA damage, P53 is activated. P53 then activates the pro-apoptotic protein Bax, which initiates the release of cytochrome C from the mitochondria. Apaf-1 and the released cytochrome C combine to form a complex known as the apoptosome. The apoptosome causes the conversion of inactive pro-caspase-9 into active Caspase-9. Caspase-9 then goes on to activate Caspase-3 in a similar manner to the extrinsic pathway. Activated Caspase-3 then leads to the Caspase cascade, resulting in apoptosis. [3]

CASPASE

The major executioners in the apoptotic programme proteases known as Caspases (cysteine dependent, aspartate-specific proteases). Caspase are cysteine proteases that are homologous to the nematode ced-3 gene product. The interleukin-1β converting enzyme (also known as Caspase 1), thefounding member of the Caspase family in vertebrates, was identified by its homology to ced-3. Thus far, 14 members of the Caspase family have been identified, 11 of which are present in humans. Caspases directly and indirectly orchestrate the morphologic changes of the cell during apoptosis. Caspases exist as latent precursors, which, when activated, initiate the death program by destroying key components of the cellular infrastructure and activating factors that mediate damage to the cells. Caspase 3 is one of important member of Caspase family. It is encoded by the CASP3 gene. Caspase-3 initiates apoptotic DNA fragmentation by proteolytically inactivating ICAD. Caspase 3 is a homo tetrameric protein. It contains 930 amino acids. (Fig. 2)

A

Caspase-3 [Homo sapiens]

GenBank: CAC88866.1

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>gi|16516817|emb|CAC88866.1| caspase-3 [Homo sapiens]
MENTENSVDSKSIKNLEPKIIHGSESMDSGMSWDTGYKMDYPEMGLCIIINNKNFHKSTGMTSRSGTDVD
AANLRETFRNLKYEVRNKNDLTREEIVELMRDVSKEDHSKRSSFVCVLLSHGEEGIIFGTNGPVDLKKIT
NFFRGDRCRSLTGKPKLFIIQACRGTELDCGIETDSGVDDDMACHKIPVDADFLYAYSTAPGYYSWRNSK
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B

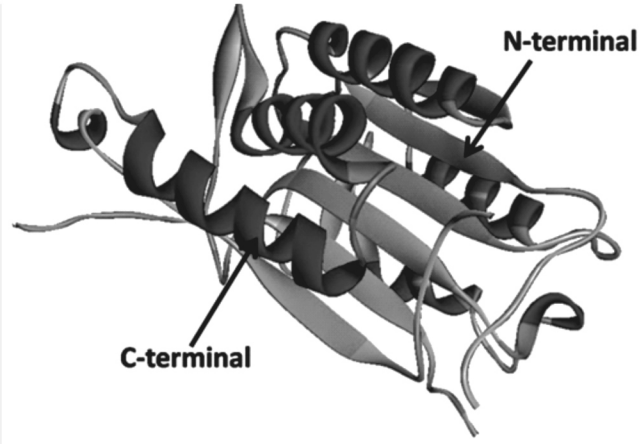


Figure 2: caspase 3 protein. A. Amino acid sequence of Caspase 3 protein,
B. N-terminal and C-terminal of Caspase 3 protein.

APOPTOSIS INHIBITORS

There are several apoptosis inhibitors present today. They inhibit the apoptosis by several path ways. The derivatives of these compounds used as anti-apoptotic compounds (Fig. 3) [4-6]

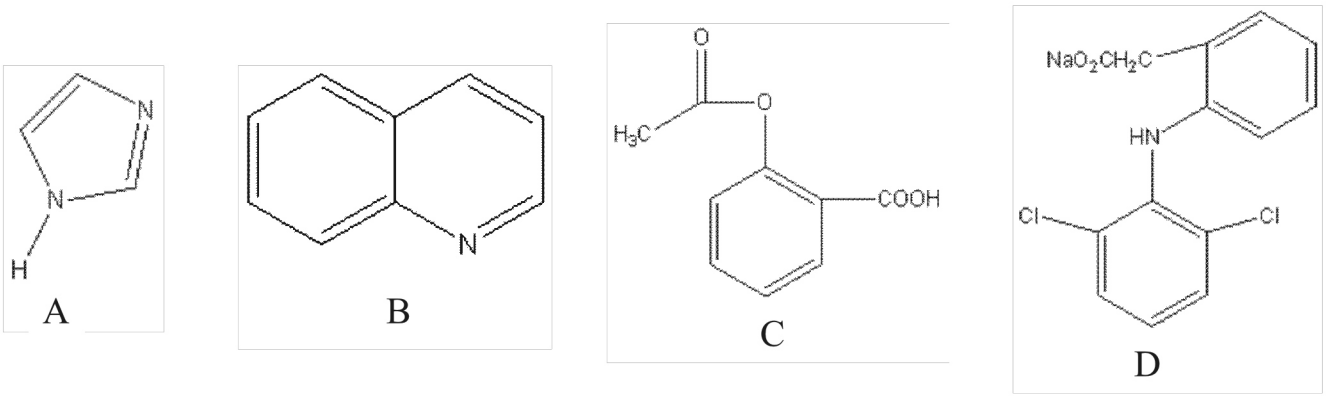


Figure 3: Anti-apoptotic compounds. A. imidazole moiety, B. Quinoline moiety,
C. Benzoic acid derivatives, and D. Di-chloro aniline derivatives

Besides these molecules, isoquinoline also has the anti-apoptotic property. Thus it could also act as caspase 3 inhibitor

ISOQUINOLINE DERIVATIVES AS CASPASE 3 INHIBITORS

Now a days, Isoquinoline derivatives are also used as caspase 3 inhibitors. There are several isoquinoline derivatives present used as anti apoptotic drug. (Fig. 4).

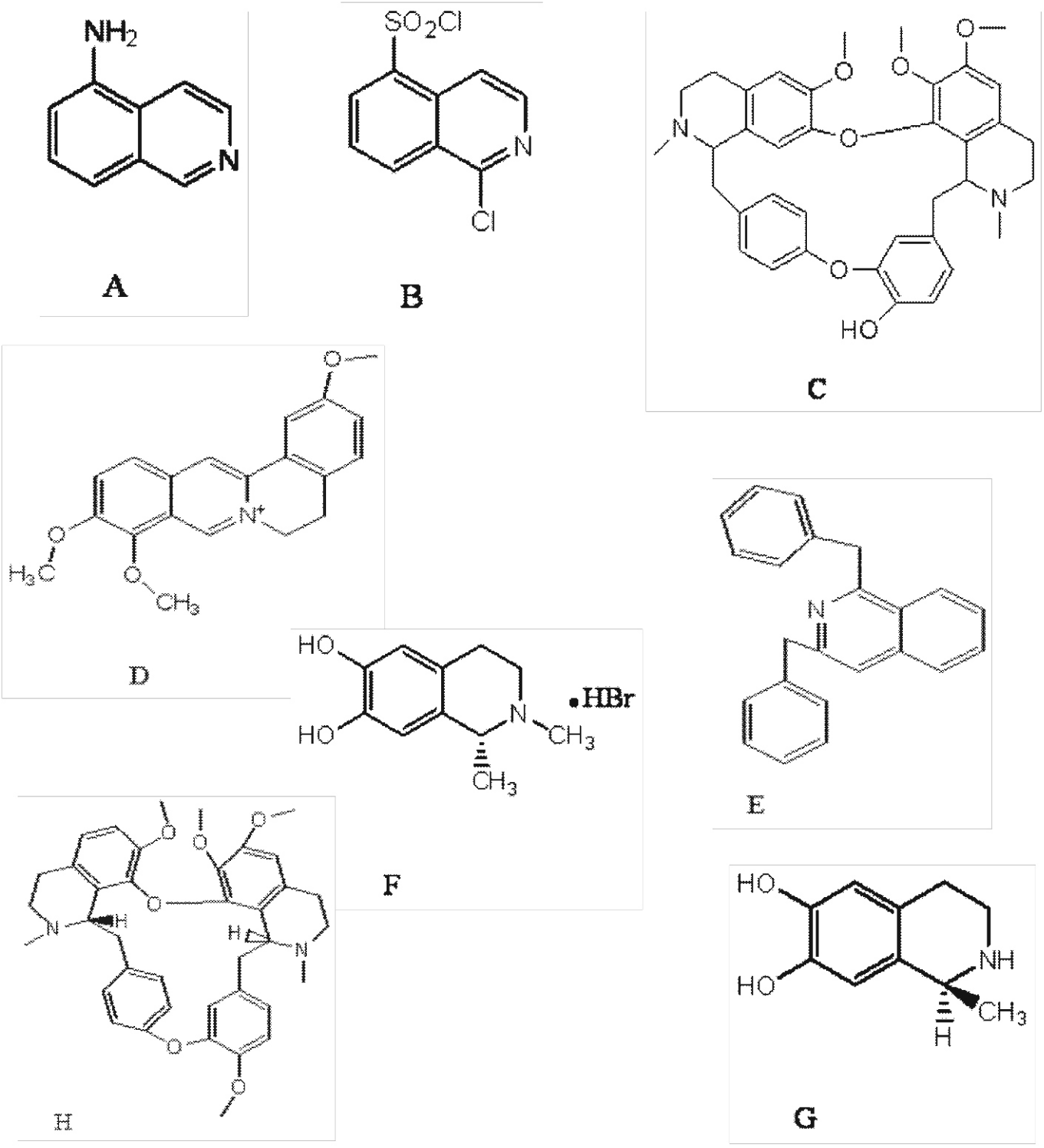
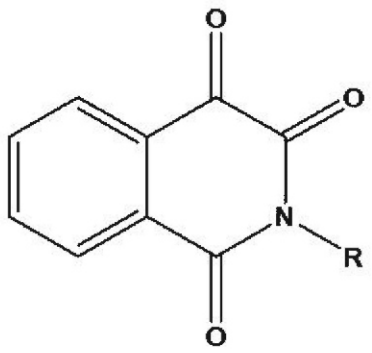


Figure 4 : isoquinoline derivatives as Caspase 3 inhibitors. A. 5-Aminoisoquinoline, B. 5-isoquinolinesulfonyl, C. Berbamine, D. Berberine, E. Bisbenzylisoquinoline, F. N-Methyl-(R)-salsolinolhydrobromide, G. Salsolinol, H. Tetrandrine.

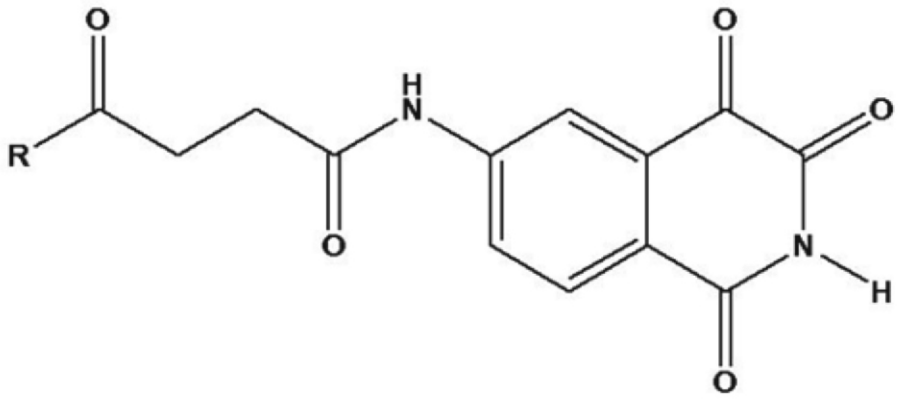


Compound 1

Table 1: IC_{50} values of some common compound 1 derivatives

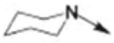
Compound	R	IC_{50} (μM)
1a	CH3-	0.255 ± 0.008
1b	CH2CHCH2-	0.261 ± 0.037
1c	C6H5CH2-	0.331 ± 0.039
1d	C6H5CH2CH2-	0.544 ± 0.016
1e	*p*-MeO-C6H4CH2-	4.63 ± 0.56
1f	*p*-F-C6H4CH2-	0.63 ± 0.26

Further Modification Based on the Scaffold of Compound 1



Compound 2

Table 2: IC_{50} values of some common derivatives of compound 2

Compd	R	IC_{50} (μM)
2a	$CH_3CH_2CH_2NH$-	0.059 ± 0.003
2b	CH_2CHCH_2NH-	0.044 ± 0.002
2c		0.025 ± 0.003
2d	BnNH-	0.070 ± 0.008
2e	PhNH-	0.201 ± 0.014
2f	*o*-MeO-C_6H_4NH-	0.113 ± 0.011
2g	*p*-MeO-C_6H_4NH-	0.158 ± 0.028
2h	*m*-MeO-C_6H_4NH-	0.148 ± 0.007
2i	*p*-F-C_6H_4NH-	0.145 ± 0.007
2j	*m*-EtO-C_6H_4NH-	0.055 ± 0.004
2k	*m*-^{n}PrO-C_6H_4NH-	0.071 ± 0.005

BIOACTIVITY OF CASPASE 3 INHIBITOR COMPOUNDS

The biochemistry of the different caspase 3 inhibitors is different. The compounds are highly potential for the inhibition of caspase 3 activity. For example; 5-isoquinolinesulfonyl : for 6k, IC_{50} = 40 nM

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